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RESPIRATORY CARE

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36TH YEAR—ESTABLISHED 1956

SPECIAL ISSUE
RESPIRATORY CARE OF INFANTS
AND CHILDREN
Part II

- Disorders of Respiratory Control
- ECMO: Where Have We Been? Where Are We Going?
- Surfactant Therapy in RDS
- Long-Term Outcome
- Transport of the Critically Ill and Injured
- Bronchial Hyperreactivity
- Cystic Fibrosis Reviewed
- 1990 Journal Conference Summary

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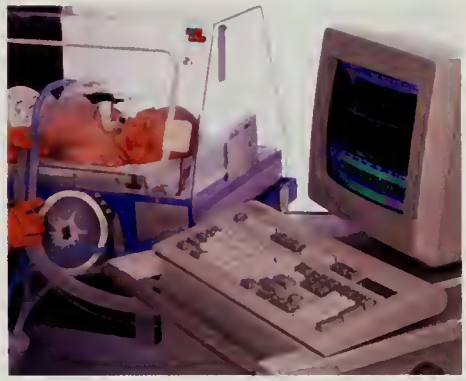

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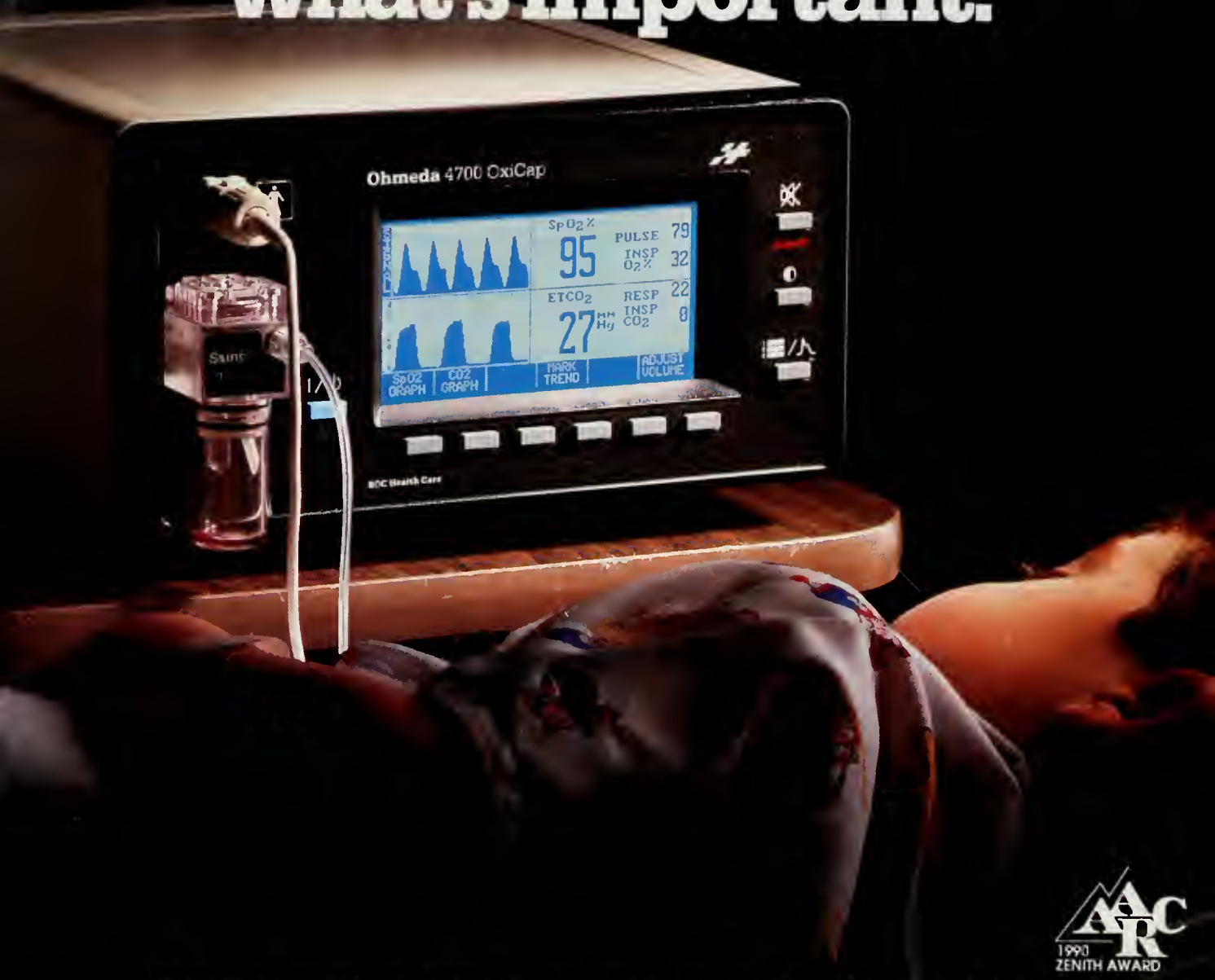

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Reviews, Editorials, and Statements To Note

Surfactant Replacement Therapy (editorial)—ME Avery, TA Merritt. N Engl J Med 1991;324:910. (Pertains to Kendig et al paper abstracted below.)

Screening for Cystic Fibrosis: Ethical and Social Issues (editorial)—E Kerem, A Lynch. Am Rev Respir Dis 1991;143:457.

Smoking Cessation and Weight Gain (editorial)—NE Grunberg. N Engl J Med 1991;324:768. (Pertains to Williamson et al paper abstracted below.)

Right Ventricular Dysfunction in Chronic Obstructive Pulmonary Disease: Evaluation and Management (review)—JR Klinger, NS Hill. Chest 1991;99:715.

A Comparison of Surfactant as Immediate Prophylaxis and as Rescue Therapy in Newborns of Less Than 30 Weeks' Gestation—JW Kendig, RH Notter, C Cox, et al. N Engl J Med 1991;324:865.

BACKGROUND: Exogenous pulmonary surfactants are administered into the trachea either to prevent respiratory distress syndrome in premature infants or to treat it. In a randomized, multicenter trial, we compared the results of surfactant therapy initiated as prophylaxis with the results of rescue therapy with surfactant. METHODS: Before birth, 479 infants with an estimated gestational age of < 30 weeks were randomly assigned to receive surfactant as prophylaxis (n = 244). The infants in the prophylaxis group received a 90-mg intratracheal dose of an exogenous calf-lung surfactant extract at the time of delivery, whereas the infants in the rescue-therapy group received 90 mg of the surfactant several hours after delivery if the fractional inspiratory oxygen concentration was at least 0.40 or if the mean airway pressure was at least 0.686 kPa (7 cm H_2O), or both. Infants in both groups received additional doses of surfactant at intervals of 12 to 24 hours if these criteria were met. RESULTS: The proportion of infants surviving until discharge to their homes was significantly higher in the prophylaxis group than in the rescue-therapy group (88 vs 80%, p = 0.028). This difference was due primarily to the longer survival of very premature infants (≤ 26 weeks' gestation) in the prophylaxis group than in the rescue-therapy group (75 vs 54%, p = 0.006). According to proportional-hazards regression analysis, the distribution of survival times was better for all infants in the prophylaxis group (p = 0.007) and for the subgroup of infants in the prophylaxis group who were delivered at 26 weeks' gestation or earlier (p = 0.0048). Infants in the prophylaxis group who were delivered at 26 weeks' gestation or earlier had a lower incidence of pneumothorax than similar infants in the rescue-therapy group (7 vs 18%, p = 0.03). CONCLUSIONS: We found a significant advantage to the administration of the initial dose of surfactant as prophylaxis rather than as rescue therapy in very premature infants.

Smoking Cessation and Severity of Weight Gain in a National Cohort—DF Williamson, J Madans, RF Anda, JC Kleinman, GA Giovino, T Byers. N Engl J Med 1991;324:739.

BACKGROUND: Many believe that the prospect of weight gain discourages smokers from quitting. Accurate estimates of the weight gain related to the cessation of smoking in the general population are not available, however. METHODS: We related changes in body weight to changes in smoking status in adults 25 to 74 years of age who were weighed in the First National Health and Nutrition Examination Survey (NHANES I, 1971 to 1975) and then weighed a second time in the NHANES I Epidemiologic Follow-up Study (1982 to 1984). The cohort included continuing smokers (748 men and 1,137 women) and those who had quit

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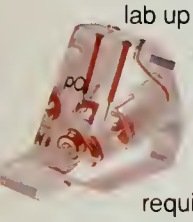

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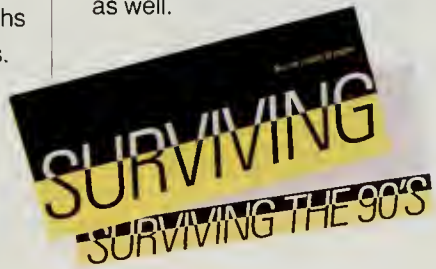

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smoking for a year or more (409 men and 359 women). RESULTS: The mean weight gain attributable to the cessation of smoking, as adjusted for age, race, level of education, alcohol use, illnesses related to change in weight, base-line weight, and physical activity was 2.8 kg in men and 3.8 kg in women. Major weight gain (> 13 kg) occurred in 9.8% of the men and 13.4% of the women who quit smoking. The relative risk of major weight gain in those who quit smoking (as compared with those who continued to smoke) was 8.1 (95% confidence interval, 3.7 to 9.1) in women, and it remained high regardless of the duration of cessation. For both sexes, blacks, people under the age of 55, and people who smoked 15 cigarettes or more per day were at higher risk of major weight gain after quitting smoking. Although at base line the smokers weighed less than those who had never smoked, they weighed nearly the same at follow-up. CONCLUSIONS: Major weight gain is strongly related to smoking cessation, but it occurs in only a minority of those who stop smoking. Weight gain is not likely to negate the health benefits of smoking cessation, but its cosmetic effects may interfere with attempts to quit. Effective methods of weight control are therefore needed for smokers trying to quit.

Helium-Oxygen Mixture in the Treatment of Postextubation Stridor in Pediatric Trauma Patients—KJ Kemper, RH Ritz, MS Benson, MS Bishop. Crit Care Med 1991;19:356.

OBJECTIVE: To assess the effectiveness of a helium-oxygen mixture in reducing post-extubation stridor in children hospitalized for burns or trauma. DESIGN: Randomized, controlled crossover trial. SETTING: Harborview Medical Center's Burn and Trauma ICUs from March to September 1989. PATIENTS: Children < 15 years old who were electively extubated and had symptoms of post-extubation stridor, but required ≤ 35% oxygen. INTERVENTION: Each treatment (helium-oxygen and oxygen-supplemented room air) was given in random order for 15 min after extubation. MEASUREMENTS: Respiratory distress was assessed by a physician blinded to treatment order using a standard stridor score and clinical judgment. RESULTS: There were 13 children with 15 extubations; seven (47%) of 15 patients required subsequent treatment with racemic epinephrine or reintubation. Stridor scores were lower with helium-oxygen than with oxygen-supplemented room air (2.8 vs 3.7, $p < 0.005$), and helium-oxygen was preferred in eight of nine trials in which one treatment was clearly favored by the physician. CONCLUSION: Because helium-oxygen therapy can reduce stridor scores and is clinically preferred by physicians caring for stridorous children, it may be a useful adjunctive therapy in pediatric trauma patients with postextubation stridor.

Individualized Aerobic and High Intensity Training for Asthmatic Children in an Exercise Readaptation Program: Is Training Always Helpful for Better Adaptation to Exercise?—AL Varray, G Mercier, M Terral, CG Prefaut. Chest 1991; 99:579.

In order to define the role of individualized training intensity in a conditioning program for asthmatic children, we have trained seven asthmatics (age = 11.4 ± 1.8 y) at their ventilatory threshold (V_{Th}) intensity level for a 3-month period (aerobic training) and at maximal intensity also for 3 months (high intensity training). V_{Th} is the point at which a nonlinear increase of $\dot{V}_E$ occurs. Another group of seven asthmatics (age = 11.4 ± 1.5 y) served as control subjects. Cardiopulmonary fitness was determined on a cycle ergometer before and after each training session. This study demonstrated that aerobic training, correctly adapted to the child's physical ability, induces the following: (1) a rapid and marked cardiovascular fitness increase; and (2) a decrease in $\dot{V}_E$ over a given work range so that V_{Th} is increased. This is of great importance because hyperventilation is a major determinant of exercise-induced bronchospasm. In contrast, even if high intensity training is well tolerated in an indoor swimming pool, the long-term effects are unsuitable for asthmatic children because the decrease of V_{Th} will involve an increase of hyperventilation, even when exercise is performed at submaximal intensity.

Adverse Health Effects among Adults Exposed to Home Dampness and Molds—RE Dales, R Burnett, H Zwanenburg. Am Rev Respir Dis 1991;143:505.

To investigate the association between home dampness and mold and health, questionnaires were administered through the primary school system to parents of school-aged children in six regions of Canada. The present report focuses on the symptoms of the 14,799 adults at least 21 years of age. The overall response rate was 83%, and missing values for individual variables ranged from 3 to 8%. The presence of home dampness and/or molds (that is, damp spots, visible mold or mildew, water damage, and flooding) was reported by 38% of respondents. The prevalence of lower respiratory symptoms (any cough, phlegm, wheeze, or wheeze with dyspnea) was increased among those reporting dampness or mold compared with those not reporting dampness or mold as follows: 38 versus 27% among current smokers, 21 versus 14% among exsmokers, and 19 versus 11% among nonsmokers (all p values < 0.001). This association persisted after adjusting for several sociodemographic variables (including

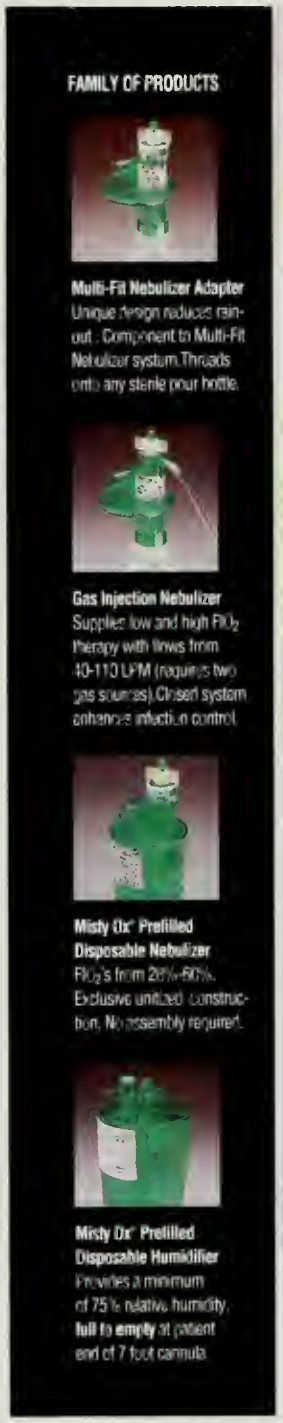
age, sex, and region) and several other exposure variables (including active and passive cigarette smoke, natural gas heating, and wood stoves). The odds ratio between symptoms and dampness was 1.62 (95% confidence interval, 1.48 to 1.78) in the final model chosen. This association persisted despite stratification by the presence of allergies or asthma. Exposure to home dampness and mold may be a risk factor for respiratory disease in the Canadian population.

Postneonatal Mortality in a Cohort of Very Low Birthweight Infants—D Bourchier, PJ Weston. NZ Med J 1991;104:11.

A cohort of very low birthweight (VLBW) infants (ie, <1500 g) who were admitted to the newborn unit, Waikato Hospital between 1984 and 1988 were followed to the age of 12 months. Four hundred and twenty-five infants were admitted with 385 surviving the neonatal period. A further 29 infants died in the postneonatal period (68.2 per 1,000 live births). Sixteen of the infants died during their initial hospitalization—primarily from complications of prematurity, while the remaining 13 died following discharge from hospital (9 from sudden infant death syndrome). The postneonatal mortality rate was 3-5 fold greater than that described in similar studies, reflecting the generally increased rate in New Zealand and a lower neonatal mortality rate. The duration of mechanical ventilation was associated with an increased risk of postneonatal death, but no risk factors for posthospital discharge death could be identified.

Aerosol Delivery in Neonatal Ventilator Circuits: A Rabbit Lung Model—D Cameron, R Arnot, M Clay, M Silverman. Pediatr Pulmonol 1991;10:208.

The benefits of inhaled therapy in ventilated neonates are recognized, but the reliability of drug delivery in nebulizer-ventilator circuits is uncertain. We quantified the effect of changing variables. Twenty-three freshly killed rabbits (1.15-1.9 kg) were ventilated via a tracheostomy by a pressure-limited, time-cycled ventilator (Neovent). A radioaerosol of $^{99}Tc^{m}$ pertechnetate from an Ultravent nebulizer (Mallinckrodt) was fed into the proximal ventilator tubing. Two 3-minute nebulizations at "standard settings" were followed by 2 at altered pressure, frequency, gas flow, I-E ratio,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MMWR 1987:36 (Suppl. No. 2S: p. 3S)

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or position of the nebulizer in the circuit. Each nebulization was followed by a 3-minute gamma camera image and total deposited radioactivity was measured in excised lungs and trachea. Images demonstrated good peripheral aerosol deposition. At standard settings, lung deposition averaged 2.8% of the aerosol released. This was decreased markedly by reducing tidal volume (ventilator pressures) and residence time of aerosol (I-E ratio). Reduced gas flow decreased deposition slightly, presumably by increased particle size and marginally reduced tidal volume. Deposition did not change with increased frequency; increased minute ventilation was offset by decreased residence time of the aerosol. We conclude that the Ultravent nebulizer can be used to nebulize drugs in a standard neonatal circuit, although the dose delivered is small. Tidal volume and aerosol residence time are important determinants of aerosol delivery.

Effect of Injected Long-Acting Epinephrine in Addition to Aerosolized Albuterol in the Treatment of Acute Asthma in Children—AE Kornberg, S Zuckerman, JR Welliver, F Mezzadri, N Aquino. Pediatr Emerg Care 1991;7:1.

The additional effect, if any, of subcutaneous, long-acting epinephrine (Sus-Phrine®) to aerosolized albuterol for acute pediatric asthma was studied. Over an 8-month period, patients were enrolled in a prospective, randomized, controlled trial. All patients were recruited and studied in a pediatric emergency department. Forty-three children between the ages of 3 and 12 years, with a mean age of 8.9 years, presenting with acute asthma were enrolled. Group 1 received Sus-Phrine®, 0.005 mL/kg before albuterol aerosols, as appropriate. Group 2 only received albuterol aerosols. There was no significant difference in the extent of improvement between the two groups at either 20 minutes or 2 hours for clinical score, peak flow, or respiratory rate. Subcutaneous, long-acting epinephrine provides no additional benefit to a beta-2 agonist by nebulization for children with acute asthma.

Inflammatory Markers in Cystic Fibrosis—RJ Rayner, MS Wiseman, SM Cordon, D Norman, EJ Hiller, DJ Shale. Respir Med 1991;85:139.

Plasma neutrophil elastase-a_1 antiproteinase complex, lactoferrin and C-reactive protein (CRP) were determined over a 15-month period in 26 patients with cystic fibrosis, of whom 21 were chronically infected with *Pseudomonas aeruginosa*. Median concentrations of both neutrophil products and CRP were greater in patients who were clinically stable than in healthy subjects without cystic fibrosis. CRP concentrations increased further at the onset of symptomatic exacerbations. Thirty-five courses of intravenous antibiotics and 22 courses of oral ciprofloxacin were reviewed and revealed similar improvements in clinical scores and lung function tests for both forms of treatment. Intravenous antibiotics reduced the plasma concentrations of both neutrophil elastase-a_1 antiproteinase complex. Plasma concentrations of inflammatory markers were significantly greater in exacerbations associated with fever and leukocytosis. Statistical modelling demonstrated negative within-patient relationships between lung function and both CRP and lactoferrin, and positive relationships between the three inflammatory markers. Neutrophil granule products and CRP reflect the pulmonary inflammatory state in cystic fibrosis and may be of value in monitoring treatment.

Acceptability and Reproducibility Criteria of the American Thoracic Society as Observed in a Sample of the General Population—JL Hankinson, KM Bang. Am Rev Respir Dis 1991;143:516.

An analysis of spirograms of 6,486 subjects from the general population, ages 8 to 90 years, was conducted to determine their ability to satisfy the American Thoracic Society's (ATS) acceptability and reproducibility criteria. The results indicate that both older and younger subjects had more difficulty satisfying the ATS acceptability and reproducibility criteria. The difficulty in satisfying the ATS reproducibility criterion, particularly in younger subjects, was in part associated with their smaller heights and lung volumes. A relatively uniform within-subject variability of FVC and FEV_1 in terms of the mean differences between the largest and second largest FVC and FEV_1, for all heights, was observed. In addition, unlike the ATS reproducibility criterion, when a constant 200-mL reproducibility criterion for FVC and FEV_1 was used, there was no longer a significant difference between the number of reproducibility criterion failures for the 14 different height groups used. These results suggest that the ATS reproducibility criterion, based on a percentage of the FVC and FEV_1, may inappropriately classify a higher percentage of subjects with smaller heights and lung volumes as having a nonreproducible test. In contrast, subjects with larger heights and lung volumes are much less likely to fail the ATS reproducibility requirement. These results emphasize the importance of following the ATS recommendation of using the reproducibility criterion only as a goal during data collection, not to classify a subject as having an invalid test.

Oxygen Desaturation during Fiberoptic Bronchoscopy in Pediatric Patients—BM Schnapf. Chest 1991;99:591.

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STUDY OBJECTIVE: Pulse oximetry was used to measure arterial oxygen saturation and the extent of hypoxemia in pediatric patients undergoing fiberoptic bronchoscopy (FB). DESIGN: Arterial oxygen saturation (S_{aO_2})was measured (1) prior to the procedure to provide a baseline value, (2) when the bronchoscope was positioned in the nasopharynx, and (3) when the bronchoscope was positioned in the mid-trachea. SETTING: Fiberoptic bronchoscopy was performed in the Pediatric Special Care Unit or in the Pediatric Pulmonary Laboratory using an Olympus BF3C4 fiberoptic bronchoscope with a 3.5-mm outer diameter. PATIENTS OR PARTICIPANTS: Thirty-six children who underwent diagnostic or therapeutic bronchoscopy for a variety of reasons were evaluated. They ranged in age from 6 to 142 months; 20 were male and 16 were female. INTERVENTIONS: There were no interventions. MEASUREMENTS AND RESULTS: Of the 36 patients, 29 experienced a fall in S_{aO_2} levels exceeding 5% of baseline values. The youngest age group, 6 to 12 months, showed the greatest drop in S_{aO_2} as compared with the other groups. Desaturation was significantly increased by mid-tracheal FB. CONCLUSIONS: A decline in S_{aO_2} that may be substantial in infants and children undergoing FB examination was frequently noted, especially in smaller infants and when the bronchoscope was positioned in the mid-trachea. Supplemental oxygen and a brisk procedure time will minimize the risk of dangerous hypoxia.

A Randomized Placebo-Controlled Study to Evaluate the Effects of Oral Albuterol on Pulmonary Mechanics in Ventilator-Dependent Infants at Risk of Developing BPD—JL Stefano, VK Bhutani, WW Fox. Pediatr Pulmonol 1991;10:183.

Albuterol is a specific beta-2 agonist that has been reported to be effective in treating infants and children with bronchospastic pulmonary disease. The use of oral albuterol has not been investigated in patients with bronchopulmonary dysplasia (BPD). Thirty premature infants were randomized to receive oral albuterol (0.15 mg/kg/dose q8h) or a volume- and color-matched placebo (D5/W). Pulmonary functions were evaluated at baseline and at 48 and 96 hours after entry to the study. The study was also designed for crossover from placebo to albuterol or albuterol to caffeine in the event that the infant's total pulmonary resistance did not improve at the time of the 48-hour pulmonary function evaluation. Heart rate and respiratory rate showed a statistically significant but clinically unimportant increase in the albuterol-treated infants. There were no significant differences noted in systolic or diastolic blood pressure. Percent improvement in the pulmonary function indices were calculated from baseline to 48 hours and from baseline to 96 hours for the placebo and albuterol-treated groups. The results indicate that at 48 hours there were statistically significant improvements in total resistance (14.5%), inspiratory resistance (10.8%), and expiratory resistance (12.9%) in the albuterol-treated infants as compared to the spontaneous deterioration of the same values by 25%, 81%, and 11%, respectively, in the placebo-treated infants. In conclusion, oral albuterol therapy of 48 hours duration improved pulmonary resistance without major cardiovascular side effects in ventilator-dependent premature infants.

Continual Trending of Fick Variables in the Critically Ill Patient—TJ Quinn, C Weissman, M Kemper. Chest 1991;99:703.

We continually monitored components of the Fick equation (oxygen consumption, arterial and mixed venous oxygen saturation) simultaneously in ten hemodynamically stable, mechanically ventilated postoperative patients in order to evaluate our ability to continually calculate cardiac output (Qc) from its Fick determinants. Qc underestimated ($p < 0.001$) cardiac output calculated from intermittent CO-oximeter measurements (6.2 vs 6.4 L/min) with good correlation ($r = 0.96$), while it consistently overestimated ($p < 0.05$) thermodilution cardiac output (Qtd) (6.2 vs 5.9 L/min, $r = 0.84$). Measured oxygen consumption correlated with Qtd ($r = 0.78$) nearly as well as did Qc, while mixed venous oxygen saturation correlated poorly with Qtd ($r = -0.10$). Trends of multiple Fick variables were helpful in interpreting changes in a single parameter. We conclude that continual trending of Fick variables in critically ill patients is both feasible and useful and that Qc agrees well with both traditional Fick cardiac output computed from CO-oximetry data and thermodilution measurements. Finally, measured oxygen consumption, available continuously, correlates well with changes in cardiac output in this subset of critically-ill patients.

Verification of Endotracheal Tube Placement with Colorimetric End-Tidal CO_2 Detection—BA MacLeod, MB Heller, J Gerard, DM Yealy, JJ Menegazzi. Ann Emerg Med 1991; 20:267.

STUDY OBJECTIVE: To determine the ability of a disposable colorimetric CO_2 detector to accurately confirm or refute endotracheal tube placement. DESIGN: Two hundred fifty prospective emergency intubations. SETTING: Emergency intubations performed in the emergency department, helicopter, and prehospital ground

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Controlled clinical trials with EXOSURF Neonatal showed "dramatic reductions" in morbidity and mortality of infants with RDS. Subsequent use under a year-long Treatment IND confirmed its efficacy and impressive safety profile. Since release for marketing in August 1990, widespread use in hospitals across the United States has further established its value in the treatment of RDS. The weight of clinical experience is in favor of EXOSURF Neonatal.

Dramatic reductions in neonatal morbidity and mortality reported in clinical trials[1-5]

Improvement in clinical outcome after EXOSURF Neonatal has been significant in infants at risk of developing RDS as well as those with established RDS. Prophylactic as well as rescue treatment with EXOSURF Neonatal has dramatically reduced morbidity and mortality in infants weighing greater than 700 grams.

SIGNIFICANT REDUCTIONS IN OVERALL MORTALITY FROM ANY CAUSE IN MIDDLE-SIZE AND LARGE INFANTS[2,5]
(Percent reductions with EXOSURF)

	Prophylactic treatment		Rescue treatment	
Age	*Single Dose*[2] 700-1100 grams (N=446)	*One vs Three Doses*[3] 700-1100 grams (N=716)	*Two Dose*[4] 700-1350 grams (N=419)	*Two Dose*[5] 1250 grams and above (N=1232)
≤10 Days	—	—	59%[§]	35%
≤28 Days	40%*	44%[‡]	52%[§]	39%[‖]
≤1 Year	44%[†]	41%[‡]	46%[§]	31%

*P=0.022. †P=0.002. ‡P<0.05. §P<0.001. ‖P=0.039. N=Number of infants enrolled in the clinical trials.

A single prophylactic dose of EXOSURF Neonatal reduced 1-year mortality by 44%. Two additional prophylactic doses provided an additional 41% reduction in 1-year mortality.[3]

SIGNIFICANT REDUCTIONS IN MORTALITY FROM RDS IN MIDDLE-SIZE AND LARGE INFANTS[2,4,5]
(Percent reductions with EXOSURF)

	Prophylactic treatment	Rescue treatment	
	Single Dose[2] 700-1100 grams (N=446)	*Two Dose*[4] 700-1350 grams (N=419)	*Two Dose*[5] 1250 grams and above (N=1232)
Reduction in death from RDS	58%*	66%[†]	63%[‡]

*P=0.011. †P=0.007. ‡P=0.009. N=Number of infants enrolled in the clinical trials.

SIGNIFICANT REDUCTION IN CARDIOPULMONARY DESTRUCTION TO DAY 28 FOLLOWING TWO-DOSE RESCUE TREATMENT[4,5]

(Percent reductions with EXOSURF)

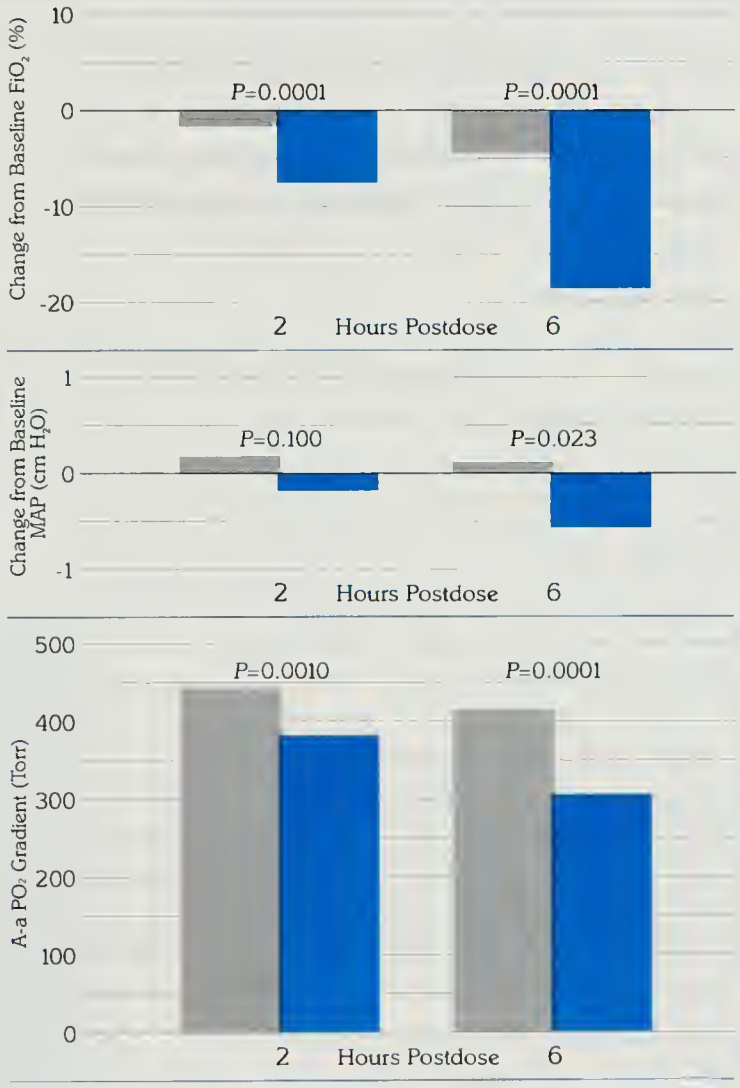
Birth weight	Reduction in death at 28 days or survival with broncho-pulmonary dysplasia (BPD)
700-1350[4] (N=419)	34%*
1250 and above[5] (N=1232)	43%*

*P=0.002. N=Number of infants enrolled in the clinical trials.

Rapid onset of action documented in rescue use[4]

Improvements in mean FiO_2 and mean alveolar-arterial PO_2 (A-a) gradient were present by 2 hours after dosing in middle-size babies (700-1350 grams). Improvements in mean airway pressures began sometime between 2 and 6 hours in middle-size babies. These improvements persisted for at least 7 days.

SIGNIFICANT IMPROVEMENTS IN SUPPLEMENTAL OXYGEN NEEDS AND VENTILATORY REQUIREMENTS SEEN IN MIDDLE-SIZE BABIES[4]



All charts from Long[4]

Please see brief summary of full prescribing information on last pages of this advertisement.

Efficacy and impressive safety profile of EXOSURF® Neonatal™ confirmed in continued widespread use[6]

In North American controlled clinical trials, more than 2600 premature infants received EXOSURF Neonatal. Under the year-long Treatment IND, over 11,400 infants received EXOSURF Neonatal. In the six months following its release for marketing, EXOSURF Neonatal has been given to 10,000 infants in more than 750 hospitals.

There are no known infectious or immunologic risks associated with EXOSURF Neonatal use. In controlled clinical trials, adverse events were comparable to those of placebo, with the exception of apnea and pulmonary bleeding. Infants receiving EXOSURF Neonatal required less ventilatory support, possibly contributing to an increased incidence of apnea. Pulmonary bleeding occurred in 1% of control infants and 2% of treated infants in controlled trials. In the treatment IND, pulmonary bleeding was reported in 4% and mucous plugging at a rate of 3/1000. Pulmonary bleeding appears to be preventable with early diagnosis and appropriate treatment of patent ductus arteriosus.

One-year follow-up evaluated developmental outcomes[7]

Double-blind 1-year follow-up of more than 1450 infants enrolled in randomized trials showed that mental and motor scores appeared to be higher in tiny infants (<750 grams) as well as middle-size infants (750-1249 grams) who received Exosurf Neonatal.

Economic data analysis showed cost savings[8-10]

Three separate studies evaluated the economic impact of a single prophylactic dose of EXOSURF Neonatal, two-dose rescue treatment in 700- to 1350-gram infants, and two-dose rescue treatment during the neonatal period in infants weighing over 1350 grams. Results indicate that both prophylactic treatment and rescue treatment are cost-effective. Mean hospital charges were $6451 less for large infants receiving two-dose rescue treatment versus air in the first 28 days of life.[10]

As easy to use as it is effective

- **Easy to store and use** EXOSURF Neonatal may be stored at room temperature. Reconstituted suspension may be maintained refrigerated or at room temperature for up to 12 hours. Key items needed for administration are supplied in one kit.
- **Easy to administer** Each EXOSURF Neonatal dose is administered in two 2.5-mL/kg half-doses without interrupting mechanical ventilation.
- **Easy on infant** To assist the distribution of EXOSURF Neonatal in the lungs, the infant is simply turned from midline position to the right after the first half-dose, and from midline position to the left after the second half-dose.

References: 1. Bose C, Corbet A, Bose G, et al. Improved outcome at 28 days of age for very low birth weight infants treated with a single dose of a synthetic surfactant. *J Pediatr.* 1990;117:947-953. **2.** Corbet A, Bucciarelli R, Goldman S, et al. Decreased mortality in small premature infants treated at birth with a single dose of synthetic surfactant: a multi-center controlled trial. *J Pediatr.* 1991;118:277-284 **3.** Gerdes J, Cook L, Beaumont E, Corbet A, Long W. American EXOSURF Pediatric Groups I and II. Effects of three vs one prophylactic doses of EXOSURF Neonatal in 700- to 1100-gram neonates. *Pediatr Res.* 1991;29(no. 4, pt 2):214A. Abstract. **4.** Long W, Thompson T, Sundell H, et al. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. *J Pediatr.* 1991;118:595-605. **5.** U.S. and Canadian EXOSURF Pediatric Study Groups. Effects of two rescue doses of EXOSURF® Pediatric in 1232 infants ≥1250 grams. *Pediatr Res.* 1990;27(no. 4, pt 2):320A. Abstract. **6.** Data on file, Burroughs Wellcome Co., 1991. **7.** Walter D, McGuinness G, Bose C, et al. Double-blind one-year follow-up in 1450 infants randomized to EXOSURF® Neonatal or air. *Pediatr Res.* 1991;29(no. 4, pt 2):270A. Abstract. **8.** Sell M, Corbet A, Gong A, et al. Economic impact of a single prophylactic dose of EXOSURF® Neonatal in 700- to 1100-gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):265A. Abstract. **9.** Mammel M, Mullett M, Derleth D, et al. Economic impact of two rescue doses of EXOSURF® Neonatal in 700-1350 gram infants. *Pediatr Res.* 1991,29(no. 4, pt 2):260A. Abstract. **10.** Schumacher R, Burchfield D, Vaughan R, et al. Economic impact of two rescue doses of EXOSURF® Neonatal in ≥1350 gram infants. *Pediatr Res.* 1991;29(no. 4, pt 2):264A. Abstract.

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For Intratracheal Suspension / 10 mL vials

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INDICATIONS AND USAGE: Exosurf Neonatal is indicated for

1 **Prophylactic** treatment of infants with birth weights of less than 1350 grams who are at risk of developing RDS (see PRECAUTIONS),

2 **Prophylactic** treatment of infants with birth weights greater than 1350 grams who have evidence of pulmonary immaturity and

3 **Rescue** treatment of infants who have developed RDS

CONTRAINDICATIONS: There are no known contraindications to treatment with Exosurf Neonatal

WARNINGS. Intratracheal Administration Only: Exosurf Neonatal should be administered only by instillation into the trachea. **General**: The use of Exosurf Neonatal requires expert clinical care by experienced neonatologists and other clinicians who are accomplished at neonatal intubation and ventilatory management. Adequate personnel, facilities, equipment, and medications are required to optimize perinatal outcome in premature infants. Instillation of Exosurf Neonatal should be performed **only** by trained medical personnel experienced in airway and clinical management of unstable premature infants. Vigilant clinical attention should be given to all infants prior to, during, and after administration of Exosurf Neonatal. **Acute Effects**: Exosurf Neonatal can rapidly affect oxygenation and lung compliance. **Lung Compliance**: If chest expansion improves substantially after dosing, peak ventilator inspiratory pressures should be reduced immediately, without waiting for confirmation of respiratory improvement by blood gas assessment. Failure to reduce inspiratory ventilator pressures rapidly in such instances can result in lung overdistention and fatal pulmonary air leak. **Hyperoxia**: If the infant becomes pink and transcutaneous oxygen saturation is in excess of 95%, FiO_2 should be reduced in small but repeated steps (until saturation is 90 to 95%) without waiting for confirmation of elevated arterial pO_2 by blood gas assessment. Failure to reduce FiO_2 in such instances can result in hyperoxia. **Hypocarbia**: If arterial or transcutaneous CO_2 measurements are <30 torr, the ventilator rate should be reduced at once. Failure to reduce ventilator rates in such instances can result in marked hypocarbia, which is known to reduce brain blood flow. **Pulmonary Hemorrhage**: In the single study conducted in infants weighing <700 grams at birth, the incidence of pulmonary hemorrhage (10% vs 2% in the placebo group) was significantly increased in the Exosurf Neonatal group. None of the five studies involving infants with birth weights >700 grams showed a significant increase in pulmonary hemorrhage in the Exosurf Neonatal group. In a cross-study analysis of these five studies, pulmonary hemorrhage was reported for 1% (14/1420) of infants in the placebo group and 2% (27/1411) of infants in the Exosurf Neonatal group. Fatal pulmonary hemorrhage occurred in three infants, two in the Exosurf Neonatal group and one in the placebo group. Mortality from all causes among infants who developed pulmonary hemorrhage was 43% in the placebo group and 37% in the Exosurf Neonatal group. Pulmonary hemorrhage in both Exosurf Neonatal and placebo infants was more frequent in infants who were younger, smaller, male, or who had a patent ductus arteriosus. Pulmonary hemorrhage typically occurred in the first 2 days of life in both treatment groups. In more than 7700 infants in the open, uncontrolled study, pulmonary hemorrhage was reported in 4%, but fatal pulmonary hemorrhage was reported rarely (0.4%). In the controlled clinical studies, Exosurf Neonatal treated infants who received steroids more than 24 hours prior to delivery or indomethacin postnatally had a lower rate of pulmonary hemorrhage than other Exosurf Neonatal treated infants. Attention should be paid to early and aggressive diagnosis and treatment (unless contraindicated) of patent ductus arteriosus during the first 2 days of life (while the ductus arteriosus is often clinically silent). Other potentially protective measures include attempting to decrease FiO_2 preferentially over ventilator pressures during the first 24 to 48 hours after dosing, and attempting to decrease PEEP minimally for at least 48 hours after dosing. **Mucous Plugs**: Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucous plugging of the endotracheal tube, particularly if pulmonary secretions were prominent prior to drug administration. Suctioning of all infants prior to dosing may lessen the chance of mucous plugs obstructing the endotracheal tube. If endotracheal tube obstruction from such plugs is suspected, and suctioning is unsuccessful in removing the obstruction, the blocked endotracheal tube should be replaced immediately.

PRECAUTIONS:

General. In the controlled clinical studies, infants known prenatally or postnatally to have major congenital anomalies, or who were suspected of having congenital infection, were excluded from entry. However, these disorders cannot be recognized early in life in all cases, and a few infants with these conditions were entered. The benefits of Exosurf Neonatal in the affected infants who received drug appeared to be similar to the benefits observed in infants without anomalies or occult infection. **Prophylactic Treatment - Infants <700 Grams**: In infants weighing 500 to 700 grams, a single prophylactic dose of Exosurf Neonatal significantly improved FiO_2 and ventilator settings, reduced pneumothorax, and reduced death from RDS, but increased pulmonary hemorrhage (see WARNINGS). Overall mortality did not differ significantly between the placebo and Exosurf Neonatal groups (see Table 1 in full product information). Data on multiple doses in infants in this weight class are not yet available. Accordingly, clinicians should carefully evaluate the potential risks and benefits of Exosurf Neonatal administration in these infants. **Rescue Treatment - Number of Doses**: A small number of infants with RDS have received more than two doses of Exosurf Neonatal as rescue treatment. Definitive data on the safety and efficacy of these additional doses are not available. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: Exosurf Neonatal at concentrations up to 10,000 µg/plate was not mutagenic in the Ames Salmonella assay. Long-term studies have not been performed in animals to evaluate the carcinogenic potential of Exosurf Neonatal. The effects of Exosurf Neonatal on fertility have not been studied.

ADVERSE REACTIONS:

General: Premature birth is associated with a high incidence of morbidity and mortality. Despite significant reductions in overall mortality associated with Exosurf Neonatal, some infants who received Exosurf Neonatal developed severe complications and either survived with permanent handicaps or died.

In controlled clinical studies evaluating the safety and efficacy of Exosurf Neonatal, numerous safety assessments were made. In infants receiving Exosurf Neonatal, pulmonary hemorrhage, apnea and use of methylxanthines were increased. A number of other adverse events were significantly reduced in the Exosurf Neonatal group, particularly various forms of pulmonary air leak and use of pancuronium. Tables 3 and 4 summarize the results of the major safety evaluations from the controlled clinical studies.

Table 3: Safety Assessments[a]—Prophylactic Treatment

Number of Doses / Birth Weight Range	Single Dose 500 to 700 grams		Single Dose 700 to 1350 grams		Single Dose 700 to 1100 grams		1 vs 3 Doses 700 to 1100 grams	
Treatment Group / Number of Infants	Placebo (Air) N=108	EXOSURF N=107	Placebo (Air) N=193	EXOSURF N=192	Placebo (Air) N=222	EXOSURF N=224	EXOSURF 1 Dose N=356	EXOSURF 3 Doses N=360
	% of Infants		% of Infants		% of Infants		% of Infants	
Intraventricular Hemorrhage (IVH)								
Overall	51	57	31	27	36	36	38	35
Severe IVH	26	25	10	8	13	14	9	9
Pulmonary Air Leak (PAL)								
Overall	52	48	16	11	32	25	29	27
Pneumothorax	23	10*	5	6	19	11*	14	12
Pneumopericardium	1	4	2	0	<1	1	1	1
Pneumomediastinum	2	1	2	3	7	1**	3	2
Pulmonary Interstitial Emphysema	43	44	13	7*	26	20	23	22
Death from PAL	4	6	<1	<1	2	1	2	1
Patent Ductus Arteriosus	49	53	66	70	50	55	59	57
Necrotizing Enterocolitis	2	4	11	13	3	4	6	2*
Pulmonary Hemorrhage	2	10**	2	4	1	4	4	6
Congenital Pneumonia	4	4	2	4	2	2	1	1
Nosocomial Pneumonia	10	10	2	4	4	7	14	15
Non-Pulmonary Infections	33	35	34	39	28	29	35	34
Sepsis	30	34	30	34	23	24	30	27
Death From Sepsis	4	4	3	3	1	2	3	2
Meningitis	4	6	3	1	2	3	1	2
Other Infections	7	4	5	3	6	10	10	11
Major Anomalies	3	1	2	4	7	4	4	4

Table 3 Safety Assessments[a]—Prophylactic Treatment (Cont.)

Number of Doses / Birth Weight Range	Single Dose 500 to 700 grams		Single Dose 700 to 1350 grams		Single Dose 700 to 1100 grams		1 vs 3 Doses 700 to 1100 grams	
Treatment Group / Number of Infants	Placebo (Air) N=108	EXOSURF N=107	Placebo (Air) N=193	EXOSURF N=192	Placebo (Air) N=222	EXOSURF N=224	EXOSURF 1 Dose N=356	EXOSURF 3 Doses N=360
	% of Infants		% of Infants		% of Infants		% of Infants	
Hypotension	70	77	52	47	59	62	54	50
Hyperbilirubinemia	22	21	63	61	27	31	20	21
Exchange Transfusion	4	3	1	2	2	2	3	1
Thrombocytopenia[b]	21	25	not available		9	8	12	10
Persistent Fetal Circulation	0	1	1	1	0	2*	1	<1
Seizures	11	8	2	2	11	9	6	5
Apnea	34	33	76	73	55	65*	62	68
Drug Therapy								
Antibiotics	96	99	98	96	98	99	>99	99
Diuretics	55	60	39	37	59	63	64	65
Anticonvulsants	14	18	23	24	20	16	9	8
Inotropes	46	40	20	20	26	20	28	27
Sedatives	62	71	65	64	63	57	52	52
Pancuronium	19	11	22	14*	19	13*	15	11
Methylxanthines	38	43	77	77	61	72*	75	82*

[a] All parameters were examined with "as-treated" analyses. * p<0.05; ** p<0.01

[b] Thrombocytopenia requiring platelet transfusion

Table 4 Safety Assessments[a]—Rescue Treatment

Number of Doses / Birth Weight Range	Two Doses 700 to 1350 grams		Two Doses 1250 grams and above	
Treatment Group / Number of Infants	Placebo (Air) N=213	EXOSURF N=206	Placebo (Air) N=622	EXOSURF N=615
	% of Infants		% of Infants	
Intraventricular Hemorrhage (IVH)				
Overall	48	52	23	18*
Severe IVH	13	9	5	4
Pulmonary Air Leak (PAL)				
Overall	54	34***	30	18***
Pneumothorax	29	20*	20	10***
Pneumopericardium	4	1	1	2
Pneumomediastinum	8	4	5	2**
Pulmonary Interstitial Emphysema	48	25***	24	13***
Death from PAL	7	3	<1	1
Patent Ductus Arteriosus	66	57	54	45*
Necrotizing Enterocolitis	3	3	1	2
Pulmonary Hemorrhage	3	1	<1	1
Congenital Pneumonia	2	3	2	2
Nosocomial Pneumonia	5	7	2	2
Non-Pulmonary Infections	19	22	13	13
Sepsis	15	17	8	8
Death From Sepsis	<1	<1	1	<1
Meningitis	1	<1	1	<1*
Other Infections	5	8	5	6
Major Anomalies	3	3	4	4
Hypotension	62	57	50	39**
Hyperbilirubinemia	17	19	12	10
Exchange Transfusion	3	4	1	2
Thrombocytopenia[b]	10	11	4	<1**
Persistent Fetal Circulation	1	1	6	2**
Seizures	10	10	6	3*
Apnea	48	65**	37	44*
Drug Therapy				
Antibiotics	100	99	98	98
Diuretics	60	65	45	34***
Anticonvulsants	17	17	10	5**
Inotropes	36	31	27	16***
Sedatives	72	68	76	64***
Pancuronium	34	17**	33	15***
Methylxanthines	62	74**	49	53

[a] All parameters were examined with "as-treated" analyses. * p<0.05; ** p<0.01; *** p<0.001

[b] Thrombocytopenia requiring platelet transfusion

Pulmonary Hemorrhage. See WARNINGS. **Abnormal Laboratory Values**. Abnormal laboratory values are common in critically ill, mechanically ventilated, premature infants. A higher incidence of abnormal laboratory values in the Exosurf Neonatal group was not reported. **Events During Dosing**. Data on events during dosing are available from more than 8800 infants in the open, uncontrolled clinical study (Table 5).

Table 5 Events During Dosing in the Open, Uncontrolled Study[a]

Treatment Type / Number of Infants	Prophylactic Treatment N=1127	Rescue Treatment N=7711
	% of Infants	% of Infants
Reflux of Exosurf	20	31
Drop in O_2 saturation (≥ 20%)	6	22
Rise in O_2 saturation (≥ 10%)	5	6
Drop in transcutaneous pO_2 (≥ 20 mm Hg)	1	8
Rise in transcutaneous pO_2 (≥ 20 mm Hg)	2	5
Drop in transcutaneous pCO_2 (≥ 20 mm Hg)	<1	1
Rise in transcutaneous pCO_2 (≥ 20 mm Hg)	1	3
Bradycardia (<60 beats/min)	1	3
Tachycardia (>200 beats/min)	<1	<1
Gagging	1	5
Mucous Plugs	<1	<1

[a] Infants may have experienced more than one event. Investigators were prohibited from adjusting FiO_2 and/or ventilator settings during dosing unless significant clinical deterioration occurred.

Reflux. Reflux of Exosurf Neonatal into the endotracheal tube during dosing has been observed and may be associated with rapid drug administration. If reflux occurs, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O until the endotracheal tube clears. ***>20% Drop in Transcutaneous Oxygen Saturation***: If transcutaneous oxygen saturation declines during dosing, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O for 1 to 2 minutes. In addition, increases of FiO_2 may be required for 1 to 2 minutes. ***Mucous Plugs***: See WARNINGS.

DOSAGE AND ADMINISTRATION. See full product information.

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environment. TYPE OF PARTICIPANTS: Intubations were performed by emergency medicine residents, paramedics, and flight nurses. INTERVENTIONS: The FEF™ CO_2 detector was applied after 250 emergency intubations. Notation of color change indicating intratracheal placement was recorded in each case. Confirmation or refutation of the detector's results was determined subsequently through traditional methods. RESULTS: The sensitivity for confirmation of endotracheal intubation in the 137 patients with a palpable pulse was 100%. However, only 76 of 103 patients (sensitivity, 72%) in cardiac arrest had endotracheal intubation confirmed by color change. The device was uniformly specific for tracheal intubation in 73 arrested patients in whom a color change was noted (100%). There was one instance (of a total of seven misintubations) in which a positive color change was noted, but the tube was not intratracheal (specificity, 86%). Overall sensitivity for tracheal intubation was 88% (95% confidence limits; range, 0.83 to 0.92), and specificity for tracheal intubation was 92% (95% confidence limits; range, 0.62 to 0.99). CONCLUSION: The FEF™ colorimetric detector reliably detects intratracheal placement in the nonarrested patient. Its use in prolonged cardiac arrest merits further study.

Pressure-Time Product during Continuous Positive Airway Pressure, Pressure Support Ventilation, and T-Piece during Weaning from Mechanical Ventilation—CSH Sassoon, RW Light, R Lodia, GC Sieck, CK Mahutte. Am Rev Respir Dis 1991;143:469.

The objective of this study was to compare the effects of continuous positive airway pressure (CPAP), pressure support ventilation (PS), and T-piece on the pressure-time product (PTP) during weaning from mechanical ventilation. The PTP is an estimate of the metabolic work or oxygen consumption of the respiratory muscles. We studied 10 intubated patients recovering form acute respiratory failure of various etiologies. A modified continuous flow (flow-by) CPAP of 0 and 5 cm H_2O (CPAP-0 and CPAP-5, respectively), PS of 5 cm H_2O (PS-5), and T-piece were applied in random order for 30 min each. In the last 5 min of the 30-min periods, we measured the esophageal pressure and transdiaphragmatic pressure-time products—PTP(es) and PTP(di), cm $H_2O \cdot s/min$, respectively—multiplied by respiratory frequency. Breathing pattern, total lung resistance (R_L), quasi-static lung compliance (C_L), intrinsic positive end-expiratory pressure ($PEEP_i$), end expiratory transpulmonary pressure (Ptpexp), arterial blood gases, blood pressure, and heart rate were also measured. In comparison to T-piece, CPAP-5 decreased PTP(es) 40% ($p < 0.01$) and PEP(di) 43% ($p < 0.02$), whereas PS-5 decreased PTP(es) 34% ($p < 0.01$) and PTP(di) 38% ($p < 0.05$). The decrease in PTP(es) with CPAP-5 was associated with a significant reduction in R_L, and to a less extent in $PEEP_i$ relative to airway pressure. The contribution of the decrease in $PEEP_i$ to the reduction in PTP(es) amounted to 36%. With PS-5, respiratory system mechanics and $PEEP_i$ were not significantly different compared with T-piece. With CPAP-0, PTP tended to be lower than with T-piece. This was likely due to the inherent small end-inspiratory positive pressure related to the CPAP system. Breathing pattern, arterial blood gas measurements, and hemodynamics were similar in all the ventilatory modes. In conclusion, during weaning from mechanical ventilation of patients recovering from acute respiratory failure, low levels of CPAP and PS significantly decrease the pressure-time product by 40 and 34%, respectively, compared with T-piece.

Predictors of Postextubation Stridor in Pediatric Trauma Patients—KJ Kemper, MS Benson, MJ Bishop. Crit Care Med 1991; 19:352.

OBJECTIVE: To determine which factors are the best predictors of postextubation stridor in pediatric trauma patients. DESIGN: Prospective cohort study. SETTING: The Burn and Trauma ICUs at Harborview Medical Center from March to September 1989. PATIENTS: Children were eligible for the study if they were <15 years old, were intubated for >12 hours, and did not have underlying cardiopulmonary disease. The study included 25 patients with 30 extubations. RISK FACTORS ASSESSED: Age, type of injury (burn vs trauma), location of intubation (field vs hospital), endotracheal tube size, length of intubation, and presence of an airleak around the tube at the time of extubation at 30 cm H_2O pressure. MAIN OUTCOME MEASURE: Moderate to severe postextubation stridor requiring treatment with racemic epinephrine, helium-oxygen, reintubation, or tracheostomy. RESULTS: Treatment for postextubation stridor was required after 11 (37%) of 30 extubations, with 5 reintubations and 1 tracheostomy. The best predictor of postextubation stridor was absence of an airleak at the time of extubation (sensitivity 100%, positive predictive value 79%, $p < 0.001$), followed by type of injury (facial burn vs all others; sensitivity 64%, positive predictive value 88%, $p < 0.001$). After controlling for these two factors, no other factor studied was a significant predictor of postextubation stridor. CONCLUSION: In pediatric trauma patients,

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mechanism of injury (facial burn vs other) and absence of an airleak at the time of extubation are the strongest factors predicting postextubation stridor. Patients with one or both risk factors require special attention to airway management.

Effect of Salbutamol on Specific Airway Resistance in Infants With a History of Wheezing—L Orlowski, C Zychowicz, M Migdal, P Gutkowski. Pediatr Pulmonol 1991;10:191.

The purpose of this study was to assess the effectiveness of nebulized salbutamol in infants with a history of wheezing. Eighty-eight children aged 3-24 months with a history of wheezing were studied, in seven groups: I (n = 15) and I/A (n = 17), with elevated specific airway resistance (sR_{aw}); II (n = 17) with normal sR_{aw}; III (n = 23), III/A (n = 17) and IV (n = 18) with normal sR_{aw} exposed to carbachol bronchial challenge (CBC); and V (n = 13) serving as control. Infants for groups I/A and III/A were selected to match by age and by baseline and post-carbachol sR_{aw} values, respectively. Baseline airway resistance and thoracic gas volume (TGV) were measured plethysmographically. Specific airway resistance was selected as an index of bronchial function. Thereafter every child in groups I, I/A, and II inhaled 200 μg of salbutamol by tidal breathing, and the children in groups III, III/A, and IV were exposed to CBC. Following positive reaction to carbachol, children of groups III and III/A inhaled salbutamol (200 μg tidal breathing), and those of group IV received no drug. Controls from group V with normal sR_{aw} received placebo (phosphate-buffered saline). Plethysmography was repeated in all children at 5 minute intervals. Following salbutamol sR_{aw} was reduced in children with elevated and normal sR_{aw}. In contrast, children not receiving salbutamol had unchanged sR_{aw} value. The response to salbutamol meaured by sR_{aw}, R_{aw}, and TGV was not significantly different in the spontaneously obstructed infants compared to those who received carbachol. In conclusion, infants with a history of wheezing do respond to inhaled salbutamol.

Analysis of Breath Sounds in Normal and Asthmatic Children and Adults Using Computer Digitized Airway Phonopneumography (CDAP)—DG Tinkelman, C Lutz, B Conner. Respir Med 1991;85:125.

Analysis of breath sounds using the stethoscope is a major part of physicians evaluation of their patients. However, the use of a stethoscope is often inadequate to give quantitative measurements of the clinical state of the individual. In this study a modification of a previously described computer analysis of breath sounds was used to measure sound intensity levels in both normal and asthmatic children who, in most cases, were unable to perform pulmonary function. The intensity levels were derived using a microcomputer-based program that digitizes audio signals and calculates energy values at 25-ms intervals throughout each signal. There were statistical differences between mean intensity levels for normal breath sounds in children between 2 and 6 years and the mean intensity levels for wheezing sounds in the same age group, as well as wheezing sounds in asthmatic patients over the age of 8 years ($p < 0.002$). Also, the mean intensity levels for normal breath sounds could be clearly differentiated from intensity levels for other sounds from the chest, including heart sounds and voice sounds. Thus, computer digitized airway phonopneumography (CDAP) proved to be a reproducible, quantifiable method

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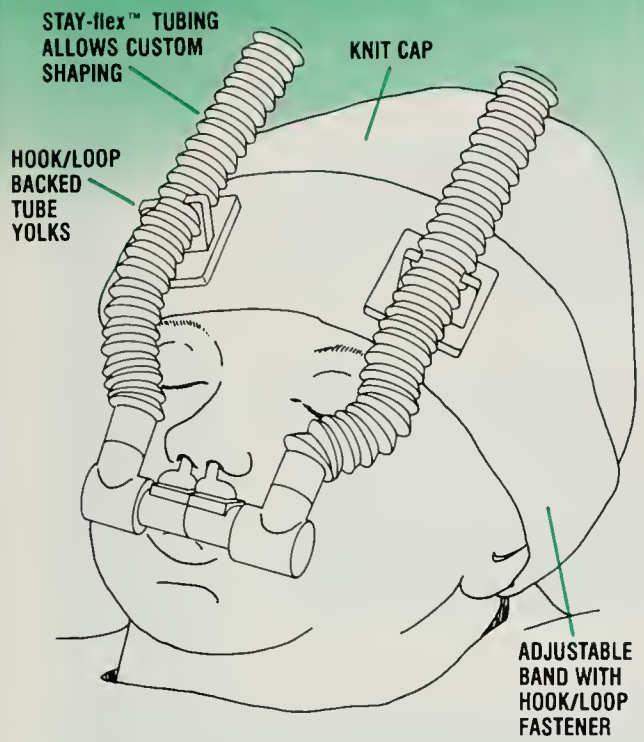

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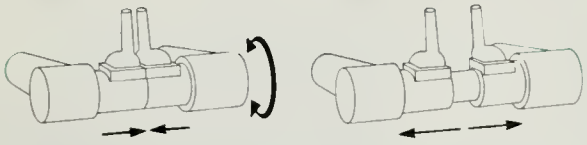

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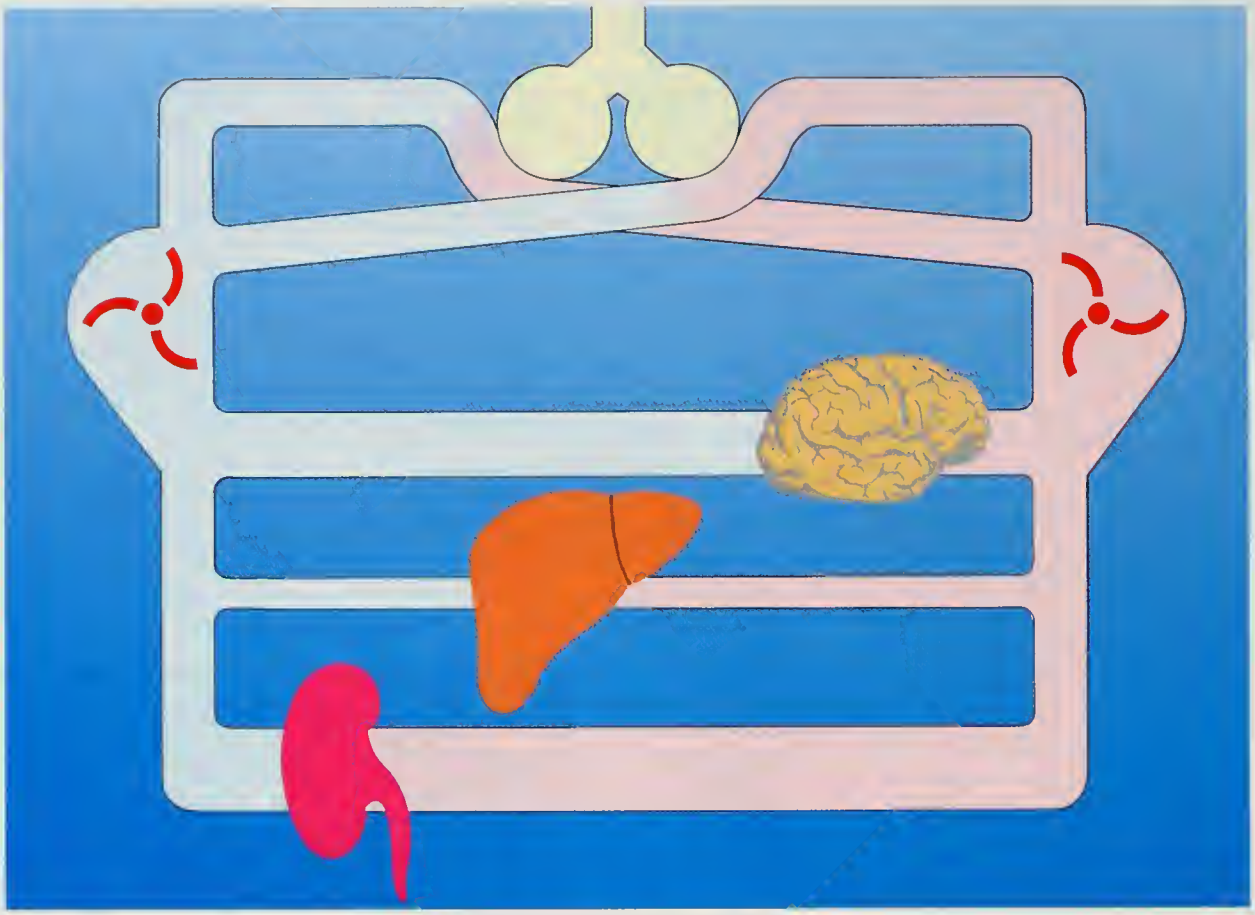

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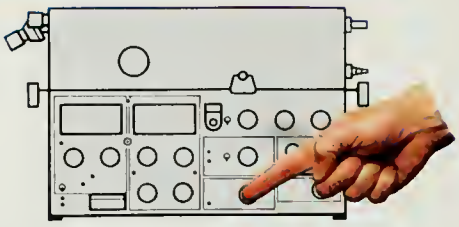

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Birthweight, Early Passive Respiratory System Mechanics, and Ventilator Requirements as Predictors of Outcome in Premature Infants With Respiratory Failure—H Kirpalani, B Schmidt, S Gaston, R Santos, R Wilkie. Pediatr Pulmonol 1991;10:195.

Early respiratory mechanics have been reported to predict outcome in newborns with respiratory failure. However, it remains unknown whether measurements of pulmonary function add significantly to the predictive value of more readily available variables such as birthweight. The present study was designed to answer this question. Passive respiratory system mechanics were measured by an airway occlusion technique in 104 ventilator-dependent premature infants between 6 and 48 hours of life and corrected for infant size. A ventilation index [$F_{IO_2} \times$ mean airway pressure (MAP)] was calculated at the time of pulmonary function testing. Poor outcome was defined as death from respiratory failure or need for supplemental oxygen at 28 days. Stepwise logistic function regression examined whether ventilation index and respiratory mechanics added predictive power over and above birthweight. Five infants died, and 45 patients required supplemental oxygen at 28 days. Birthweight was a strong predictor of outcome ($p < 0.00005$) and would have entered the logistic model first in any case. Ventilation index added significantly to the predictive model ($p = 0.038$). Respiratory system conductance ($p = 0.15$) and compliance ($p = 0.93$) entered on the third and last step, respectively. We conclude that in premature infants with respiratory failure, birthweight is a strong predictor of outcome. Early ventilator requirements but not respiratory system mechanics, add significantly to this predictive model.

Advance Directives for Medical Care—A Case for Greater Use—LL Emanuel, MJ Barry, JD Stoeckle, LM Ettelson, EJ Emanuel. N Engl J Med 1991;324:889.

BACKGROUND: Advance directives for medical care and the designation of proxy decision makers to guide medical care after a patient has become incompetent have been widely advo-

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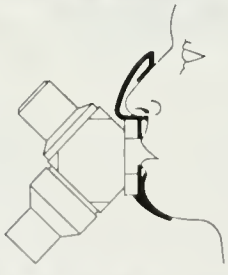

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cated but little studied. We investigated the attitudes of patients toward planning, perceived barriers to such planning, treatment preferences in four hypothetical scenarios, and the feasibility of using a particular document (the Medical Directive) in the outpatient setting to specify advance directives. METHODS: We surveyed 405 outpatients of 30 primary care physicians at Massachusetts General Hospital and 102 members of the general public in Boston and asked them as part of the survey to complete the Medical Directive. RESULTS: Advance directives were desired by 93% of the outpatients and 89% of the members of the general public ($p > 0.2$). Both the young and the healthy subgroups expressed at least as much interest in planning as those older than 65 and those in fair-to-poor health. Of the perceived barriers to issuing advance directives, the lack of physician initiative was among the most frequently mentioned, and the disturbing nature of the topic was among the least. The outpatients refused life-sustaining treatments in 71% of their responses to options in the four scenarios (coma with chance of recovery, 57%; persistent vegetative state, 85%; dementia, 79%; and dementia with a terminal illness, 87%), with small differences between widely differing types of treatments. Specific treatment preferences could not be usefully predicted according to age, self-rated state of health, or other demographic features. Completing the Medical Directive took a median of 14 minutes. CONCLUSIONS: When people are asked to imagine themselves incompetent with a poor prognosis, they decide against life-sustaining treatments about 70% of the time. Health, age, or other demographic features cannot be used, however, to predict specific preferences. Advance directives as part of a comprehensive approach such as that provided by the Medical Directive are desired by most people, require physician initiative, and can be achieved during a regular office visit.

New Method for Monitoring Pulmonary Artery Catheter Location—T Santora, W Ganz, J Gold, et al. Crit Care Med 1991;19:422.

OBJECTIVE: To test the ability of a modified pulmonary artery (PA) monitoring catheter to detect distal catheter migration. DESIGN: Prospective nonrandomized trial. PATIENTS: Surgical ICU patients requiring invasive hemodynamic monitoring. INTERVENTIONS: Eight patients received PA catheters modified to include a right ventricular (RV) pressure monitoring port located 7 cm from the tip. Fifteen patients received catheters with an RV port located 10 cm from the tip. Guided by the RV port pressure waveform, catheters were initially positioned so that the RV port was located just proximal to the pulmonic valve. MEASUREMENTS AND MAIN RESULTS: Pulmonary capillary occlusion pressure (PAOP) could not be obtained in six of the eight patients receiving the 7-cm RV port catheter unless the RV port was advanced into the PA. PAOP was consistently obtained in all 15 patients receiving the 10-cm RV port catheter, with the RV port positioned in the RV. Chest radiographs confirmed a central PA catheter position. In this group, distal migration of the catheter occurred 14 times in eight patients, as detected by appearance of a PA pressure waveform at the RV port. Distal migration was corrected by withdrawal of the catheter until an RV waveform reappeared at the RV port. CONCLUSIONS: We conclude that distal catheter migration occurs frequently with PA monitoring catheters, but can be detected at the bedside with a catheter modified to include an RV port 10 cm from the tip. This new catheter may add a margin of safety to PA monitoring and lower its overall cost by eliminating the need for chest radiographs ordered solely to confirm catheter tip location.

Variability of Breathlessness Measurement in Patients with Chronic Obstructive Pulmonary Disease—MJ Belman, LR Brooks, DJ Ross, Z Mohsenifar. Chest 1991;99:566.

The purpose of our study was to evaluate the reproducibility of a Borg rating of dyspnea in patients with COPD. We examined nine patients with COPD who performed a SST on 4 separate days within a 10-day period. The patients walked on a treadmill for 6 min. At the end of each minute, patients matched a Borg rating to the intensity of their breathlessness. We measured the HR, $\dot{V}_E$, $\dot{V}_{O_2}$, V_T and f at the end of each minute. While the mean $\dot{V}_{O_2}$, $\dot{V}_E$, HR, V_T, and f stabilized after one or two attempts, the Borg ratings decreased with successive tests. We conclude that the Borg scale for measuring breathlessness shows progressive decreases with repetition whereas $\dot{V}_{O_2}$, $\dot{V}_E$, HR, V_T, and f stabilize after one or two practice attempts. This suggests that desensitization to dyspnea may play a role in the improvement of patients after exercise.

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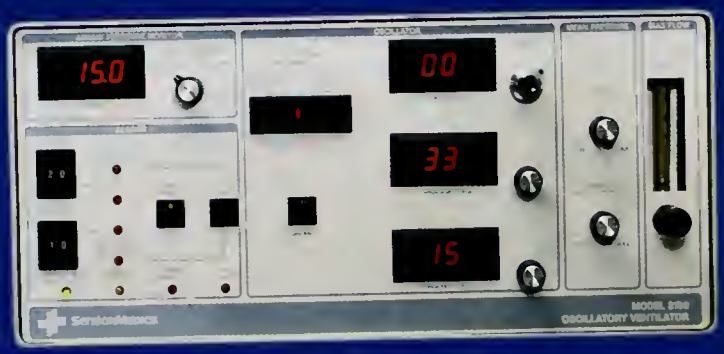

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A Learning Opportunity—*CRCE through the Journal*

It is safe to say that any respiratory care practitioner who has been away from formal training for some length of time, practices his skills differently than when his professional education was still in progress. Some of those changes can be attributed to situational factors, but most can be attributed to the effects of continuing education.

When *CRCE through the Journal* was introduced 2 years ago, it was promoted as a membership benefit. It offered members an opportunity to earn 6 hours of continuing education credit if they scored 70% or better on a 50-item test. The test itself was based on papers published in RESPIRATORY CARE during the preceding 12 months. The objective was to reward members for the learning that took place as they read the Journal.

The first year the program was offered, 1,114 readers took advantage of it. Exactly 1,000 of these answer sheets submitted had scores of 70% or better. In 1990, 854 answer sheets were sent in with 188 participants failing. The failure rate indicates that this is not a simple test. The questions are challenging but fair. The substance of the questions focuses on the most important basic concepts presented in each paper. The idea is to provide adult learners with an opportunity to read carefully and critically and to recognize they are doing so.

The tremendous opportunity that this sort of program offers cannot be overstated. As licensure spreads across the country, mandated continuing education will bring increased pressure on practitioners to pursue continuing education opportunities to meet public accountability demands established in the statutes. *CRCE through the Journal* is available to members at no cost, a critical issue during these times of budgetary constraints.

It is doubtful that practicing respiratory therapists have taken the time to stop and analyze their learning style to determine what suits them best. A student is rarely given the opportunity to elect a learning strategy, but the practitioner has that luxury. The assumption that learning only occurs in a group setting surrounded by your peers and other members of the health care team is erroneous. Learning occurs whenever and wherever knowledge is gained that leads to the solution of a problem.

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Director of Education
American Association for Respiratory Care
Dallas, Texas

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Part II

A Special Issue

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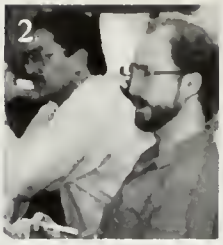

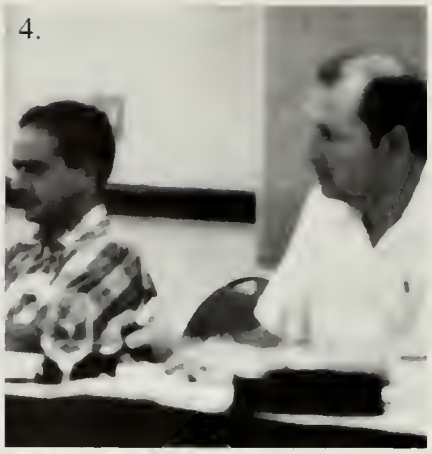

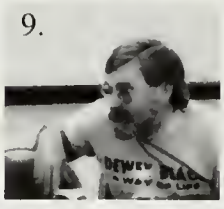

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Disorders of Respiratory Control in Infants

Ann R Stark MD

The recurrent apnea that commonly occurs in premature infants is a disorder of respiratory control. It is a frequent clinical problem and may be associated with morbidity. Although the specific etiology of this disorder is uncertain, expanded knowledge of respiratory control and its development has increased our understanding of factors that contribute to recurrent apnea and provides the basis for a rational approach to therapy.

An apneic episode, or spell, is usually defined as the cessation of airflow for 20 seconds or longer or a shorter pause in airflow that is accompanied by bradycardia (defined in the newborn as a heart rate < 100 beats/min) or cyanosis. In a study of closely monitored infants ranging in gestational age from 26 to 35 weeks,[1] the interval between the onset of apnea and the onset of bradycardia was about 8 seconds, although heart rate reached its lowest value about 29 seconds after the onset of apnea. Transcutaneous oxygen tension (P_{tcO_2}) was stable prior to the onset of most apneic episodes. P_{tcO_2} began to decline soon after the onset of apnea, and continued to fall for an average of 26 seconds after breathing efforts were re-established. Recovery of P_{tcO_2} to baseline levels occurred slowly, taking nearly 2 minutes. In another study,[2] cerebral blood-flow velocity measured in the anterior cerebral arteries by transcutaneous Doppler technique decreased markedly during apnea associated with severe bradycardia (defined as heart rate < 80 beats/min). These changes in cerebral hemodynamics appear to reflect the observed decreases in systemic blood pressure that accompany apneic spells. These findings suggest that recurrent apnea may result in ischemic brain injury.

Apneic spells occur frequently in premature infants, but their incidence decreases with increasing gestational age. The most comprehensive data available on the incidence and duration of recurrent apnea are from the study by Henderson-Smart.[3] In this study, records of more than 25,000 infants born during a 6-year period were reviewed. Of these infants, 249 (1%) had recurrent apnea, defined as 3 or more apneic episodes of > 20-second duration. In the last 2 years of the study, incidence of apnea was 78% at 26-27 weeks gestation, 75% at 28-29 weeks gestation, 54% at 30-31 weeks gestation, and 7% at 34-35 weeks gestation. These data likely underestimate the incidence of apnea in surviving infants at earlier gestational ages—in our experience, nearly all infants born before 26 weeks gestation develop recurrent apnea. In contrast, apnea rarely occurs in infants born at term (37-41 weeks gestation), and is always considered abnormal when it does occur. In these mature infants, a serious contributing cause of the apnea is usually identified (such as severe birth asphyxia, seizures, intracranial hemorrhage, or medication-induced respiratory depression). Infants who fail to breathe at birth in the absence of drug depression or asphyxia generally have irreversible structural abnormalities of the central nervous system.[4]

Apneic spells usually begin during the first 2 days of life.[3] If they do not begin during the first week of life, they are unlikely to occur later unless illness develops. In preterm infants with lung disease, apnea may not be detected until mechanical ventilation is discontinued. Apnea can persist postnatally for variable amounts of time. In most infants (> 92%

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A version of this paper was presented by Dr Stark on December 14, 1990, at the RESPIRATORY CARE Journal Conference on Respiratory Care of Infants and Children held in Cancun, Mexico.

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Abbreviations Used in This Paper

CPAP	—Continuous positive airway pressure
P_{etCO_2}	—End-tidal carbon dioxide tension (pressure)
P_{tcO_2}	—Transcutaneous oxygen tension
PSR	—Pulmonary stretch receptors
REM	—Rapid eye movement
SIDS	—Sudden-infant-death syndrome
t_e	—Duration of expiration
t_i	—Duration of inspiration

in Henderson-Smart's study[3]), apneic spells cease by 37 weeks postconception.

Mechanisms

A number of factors can contribute to the pathogenesis of apnea.[5] These factors include immaturity, influences from higher centers, neuromodulators, mechanoreceptors, reflexes from the upper airway, and central and peripheral chemoreceptors (Fig. 1). These factors exert influence on the central pattern generator, the part of the medulla in which the respiratory neurons thought to control rhythmic breathing are located. Our knowledge of how these influences interact to result in breathing-control disturbances is derived from clinical observations of factors known to precipitate the development of apnea, studies of the responses of human infants to a number of respiratory stimuli, and extrapolations from the results of invasive studies in animals.[5]

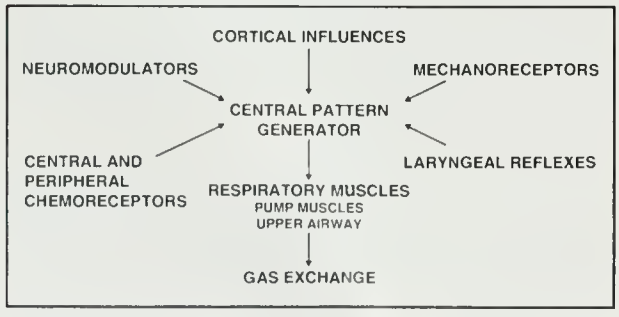

Fig. 1. Factors that may contribute to the pathogenesis of apnea by influencing the central pattern generator.

Developmental Immaturity

Evidence that developmental immaturity contributes to the pathogenesis of apnea comes from epidemiologic, anatomic, and physiologic observations. The important role of maturation is suggested by the high prevalence of apnea in infants born at low gestational ages. With increasing gestational age, the likelihood of apnea decreases. The immature brain has fewer synaptic connections, fewer dendritic arborizations, and poor myelination compared to older infants.[3] As the brain matures anatomically, stability of breathing pattern improves—suggesting that a relationship exists between anatomic development and maturation of respiratory control.

Physiologic evidence also exists for a relationship between clinical apnea and brain-stem neuronal function in infants. Henderson-Smart et al[6] observed that brain-stem conduction times of auditory-evoked responses decreased with advancing postconceptional ages between 30 and 37 weeks. In addition, between 32 and 35 weeks, infants with apnea had longer conduction times than did infants without apnea. These findings suggest that immaturity of brain-stem function may contribute to abnormal respiratory control.

Developmental changes in breathing patterns may influence the duration of breathing pauses. Regularly occurring oscillatory cycles of waxing and waning ventilation occur in sleeping infants.[7] Apnea is associated with the minimum phase of these cycles, and may be an expression of instability of the respiratory control system. Oscillatory patterns of breathing have been observed to occur more often and with greater amplitude in premature infants than in full-term infants. The longer apneic episodes observed in premature infants were related to longer cycle times and stronger breathing patterns.

Neuromodulators

A variety of neuromodulators have been identified that influence respiratory control in the newborn.[8] The role of these neuromodulators has been studied in animal preparations by direct application of the substances to parts of the brain; an effect on ventilation has been observed that may be blocked by another substance. This effect has been observed

for neuromodulators that inhibit breathing (such as endorphins, prostaglandins, and adenosine, which are blocked by naloxone, indomethacin, and theophylline, respectively). Substances that excite ventilation (including substance P and other neuropeptides such as thyrotropin-releasing hormone) have also been identified. It is possible that an imbalance between excitatory and inhibitory neuromodulators causes respiratory control instability in newborn infants.

Sleep State

Changes in sleep state have a profound influence on breathing in the newborn infant.[9] With increasing physiologic development, sleep states become more organized. For example, rapid-eye-movement (REM) and non-REM sleep cannot be differentiated using electroencephalographic criteria until infants are nearly at term. In premature infants, discriminating between sleep states can be difficult. Behavioral criteria can be used to differentiate between active (REM) and quiet sleep at about 32 weeks gestation. Using these criteria, premature infants spend up to 65% of sleep time in active sleep, about 15% in undifferentiated or indeterminate sleep, and the remainder in quiet sleep.[10] A term infant spends less time in active sleep. Breathing during active sleep tends to be highly irregular in both tidal volume and frequency, while breathing during quiet sleep is more regular. Also, more apnea occurs in active sleep than in quiet sleep.

The increased frequency of apnea during active sleep is likely the result of central neural mechanisms that affect the central pattern generator. In addition, a number of other mechanisms increase the likelihood of apnea in premature infants during active sleep.[11] Intercostal muscle activity is depressed during active sleep, resulting in paradoxical movement of the chest wall (during inspiration the rib cage moves inward and the abdomen expands). Diaphragmatic activity increases during REM sleep to compensate for the loss of the intercostal muscle contribution to ventilation.[12] Furthermore, a substantial proportion of diaphragmatic work is expended (wasted) on chest-wall distortion.[13] At the extreme, this may lead to diaphragm fatigue.[12] An increase in the transdiaphragmatic pressure gradient results in greater negative pharyngeal pressure during inspiration. This may potentiate collapse of the upper airway and result in more obstructive apnea. In addition, mechanisms to maintain end-expiratory lung volume greater than the relaxation volume determined by opposing elastic recoils of the lungs and chest wall appear to be relatively disabled in premature infants during active sleep.[14] This may lead to increased atelectasis and decreased oxygen stores, resulting in less reserve in the face of apneic spells.

Mechanoreceptors

Mechanoreceptors in the lungs and chest wall mediate reflexes that relate lung volume to respiratory cycle timing. Of particular importance are the Hering-Breuer reflexes, through which vagally mediated input from pulmonary stretch receptors (PSR) acts to change the duration of inspiration (t_i) or expiration (t_e) in response to changes in lung volume. The Hering-Breuer response is often tested by measuring the duration of an inspiratory effort made during airway occlusion at end-expiration. Because no increase in lung volume occurs, and thus no stimulation of PSR activity that would limit t_i, the t_i of an occluded effort is expected to be longer than that of the preceding control breath. This may be expressed as the percent prolongation.

The timing response to total occlusions has a developmental pattern. In one study of infants who ranged in gestational age from 25 to 40 weeks,[15] percent prolongation increased progressively with increasing gestational age. The most premature infants often shortened the duration of their occluded inspiratory efforts rather than lengthening the duration. This was likely the result of other mechanoreflexes that acted to shorten the duration of inspiration in response to inward distortion of the rib cage.[16] In contrast, the relative timing prolongation—to smaller decreases in tidal volume induced by application of single-breath mechanical loads—was comparable in healthy premature infants and term infants of similar postnatal age.[17]

The occlusion response has also been compared in premature infants with and without apnea, matching the groups for gestational (about 30 weeks) and postnatal age (about 1 week).[18] Infants with

apnea exhibited shorter duration of inspiration (with and without occlusion) than did infants without apnea. Half of the infants in the apnea group shortened t_i in response to occlusion, so that the percent prolongation was small and variable. In this study, none of the infants without apnea shortened t_i with occlusion. This suggests that infants without apnea have a more mature respiratory-reflex response, resulting in an increased ability to compensate for occlusion.

Respiratory Muscle Coordination

Ineffective breathing may result from impaired coordination of the inspiratory pump muscles (diaphragm and intercostal muscles) and the muscles of the upper airway (larynx and pharynx). Upper-airway obstruction plays a role in many spontaneously occurring apneic episodes in premature infants. In one study,[19] about 55% of apneas were identified as central, in which both diaphragm activity and airflow ceased. About 12% of apneas were considered obstructive because phasic diaphragm activity was observed in the absence of airflow. The remaining apneas were mixed, with a central pause preceding or being followed by obstructed efforts. Depressed upper-airway activity resulting in obstructive apnea may also be related to a failure of central rhythmicity.

A developmental effect on coordination of the upper-airway and pump muscles can be detected in an altered sequence of activation of the diaphragm and the laryngeal abductor muscle (posterior cricoarytenoid, PCA). A disruption of the expected sequence of activity has been observed in premature human infants and to a lesser extent in term infants.[20] This type of disruption appears to occur more commonly in newborns than it does in older animals.[21] This lack of coordination of the diaphragm and laryngeal abductor muscle appears to be well tolerated in healthy premature infants, but may contribute to decompensation in immature infants with increased respiratory demands or decreased respiratory muscle reserve.

The site of spontaneously occurring obstruction during apnea appears to be the pharynx.[22] Apneic spells occur more frequently when premature infants assume a position in which the neck is flexed, presumably because the already vulnerable neonatal airway becomes more narrow.[23] The genioglossus muscle plays a role in maintaining upper airway patency. If the activity of the genioglossus and other upper-airway muscles is decreased, negative pressure in the pharynx—generated during inspiration—may cause pharyngeal collapse. Activation of the genioglossus muscle has been observed to occur at the time spontaneous apnea resolves.[24]

The response of the genioglossus muscle to airway occlusion may be different in premature infants with apnea than it is in premature infants without apnea. Although genioglossus electromyographic activity cannot always be detected during regular breathing, activity can often be evoked by airway occlusion. Gauda et al[25] detected genioglossus activity during airway occlusion more frequently in infants without apnea than in infants with apnea.

Laryngeal Reflexes

Reflexes invoked by stimulation of the pharynx or larynx may contribute to the development of apnea. Some apneic spells may be part of an upper-airway protective reflex response to stimulation of laryngeal chemoreceptors by liquids such as water, secretions, or milk—a reflex that is potent in newborn animals.[26] The three components of this response are swallowing, airway obstruction, and central apnea. This response has been demonstrated after infusion of a small bolus of saline into the pharynx of premature infants.[27] The same pattern also has been observed during spontaneously occurring apneic spells. These observations suggest that airway-protective reflexes mediated by laryngeal chemoreceptors may play a role in some apneic spells.

Chemoreceptors

A standard technique used to evaluate the chemical control of breathing consists of measuring the changes in ventilation that occur in response to breathing different mixtures of carbon dioxide or oxygen. Developmental differences have been observed in the ventilatory responses to both hypercarbia and hypoxia.

Premature infants breathing increased levels of CO_2 have been observed to exhibit increases in tidal volume but not sustained increases in respiratory frequency. However, premature infants may exhibit variable responses to CO_2 breathing, with some showing minimal increases in ventilation.[29] In one study,[30] premature infants (30 weeks gestation) with apnea were observed to have both a substantially decreased ventilatory response to CO_2 and an increased baseline value of end-tidal carbon dioxide tension (P_{etCO_2}) compared to infants without apnea. This decreased sensitivity to CO_2 may represent greater central immaturity in the infants with apnea, although decreased respiratory muscle function may also play a role.

The response of newborn infants to breathing low concentrations of oxygen is also different from the adult response.[31,32] Although it has been observed that adults respond to a hypoxic challenge with hyperventilation, premature infants respond with a brief increase in ventilation, followed by a subsequent fall to levels that are often less than the resting level of ventilation. This response to hypoxia is generally considered to result from initial chemoreceptor stimulation followed by hypoxic depression of the respiratory center. After 2 to 3 weeks of postnatal development, the premature infant can sustain a hyperventilatory response to hypoxia similar to that of the older infant.[31] It is possible that the development of apneic spells may be partially a result of the inability of premature infants to sustain a hyperventilatory response to hypoxia.

Monitoring and Evaluation

Because of the high incidence of apnea in premature infants, all infants less than 35 weeks gestational age should be monitored for at least the first week of life.[33] Because impedance apnea monitors do not always distinguish obstructed efforts with absent airflow from normal breaths,[34] heart rate should be monitored in addition to or instead of respiration. Oxygen saturation monitoring may be of additional value.

A number of clinical conditions may contribute to the development of apneic spells in premature infants (Table 1). After the first apneic spell, the infant should be evaluated to determine the underlying cause. Clinical judgment must determine the extent of the evaluation. Apnea occurring in the term or near-term infant is always considered abnormal and is usually associated with a serious identifiable cause.

Table 1. Evaluation of an Infant with Apnea

Possible Causes	Associated Signs	Investigation
Infection	Lethargy, respiratory distress, temperature instability	Complete blood count, sepsis evaluation
Metabolic disorder	Poor feeding, lethargy, jitteriness	Glucose, calcium, electrolyte levels
Impaired oxygenation	Respiratory distress, tachypnea, cyanosis	Oxygen monitoring, arterial blood gas, chest radiograph
Maternal drugs	Maternal history, hypotonia, CNS depression	Magnesium level, urine screen for drugs
Intracranial pathology	Abnormal neurological exam, seizures	Cranial ultrasound
Environmental	Lethargy	Monitor temperature of baby and environment
Gastroesophageal reflux	Feeding difficulty	Specific observation, barium swallow

Approaches to Treatment

A number of therapeutic interventions are available for the management of infants with apnea (Table 2). If an underlying cause is identified, specific therapy should be instituted. For example, if intermittent hypoxemia is identified by transcutaneous oxygen monitoring or pulse oximetry, supplemental oxygen should be provided to maintain an adequate oxygen saturation (> 90%). In addition, care should be taken to avoid triggering reflexes that may result in apnea. Thus, oral feeding should be avoided and pharyngeal suctioning should be performed with care. Similarly, positions of extreme flexion of the neck should be avoided to minimize potentiation of airway obstruction. In some infants, lowering the environmental temperature to the low end of the neutral-thermal-environment range may decrease the frequency of spells.[35]

In a premature infant who is otherwise healthy, sensory stimulation alone (such as rubbing the feet) may be sufficient to interrupt an apneic spell. Infants who do not respond to tactile stimulation may require resuscitation with bag-mask ventilation. In some infants, prophylactic cutaneous tactile stimulation with an irregularly oscillating water bed may reduce the number of apneic spells. However, oscillating water beds do not appear to reduce residual apnea in infants receiving theophylline.[36]

Table 2. Treatment Strategies for Infants with Apnea

Treatment	Rationale
Treat underlying cause if identified	Removes precipitating factor
Tactile stimulation	Increases respiratory drive by sensory stimulation
Continuous positive airway pressure	Reduces mixed and obstructive apnea by splinting the upper airway
Theophylline	Increases respiratory center output and CO_2 response, enhances diaphragm strength; adenosine antagonist
Doxapram	Stimulates respiratory center and peripheral chemoreceptors
Transfusion	Decreases hypoxic depression by increasing oxygen carrying capacity
Mechanical ventilation	Provides support when respiratory effort is inadequate

Continuous positive airway pressure (CPAP) at 2-5 cm H_2O, administered through nasal prongs, has been used to treat apnea.[37] In the laboratory, CPAP has been observed to decrease obstructive and mixed but not central apnea.[38] It is likely that CPAP prevents obstruction by splinting open the upper airway. However, the additional airway care required and feeding difficulties frequently encountered with CPAP may limit the use of this modality.

Pharmacologic treatment with the methylxanthines theophylline[39] and caffeine[40] has been shown to reduce the number of apneic spells. Several possible mechanisms may be responsible for this effect that methylxanthines exert. Theophylline treatment stimulates respiratory center output[41] and increases the ventilatory response to CO_2,[42] possibly by increasing levels of cyclic AMP in the brain stem. Theophylline also may act by antagonizing the action of adenosine,[43] a neuromodulator that inhibits breathing, and by enhancing the strength of diaphragmatic contraction[44] (although this action has not been demonstrated in premature infants). Theophylline also has been observed to increase the metabolic rate;[45] therefore, its usefulness may be limited in low-birthweight infants with nutritional problems.

Apneic infants who fail to respond to methylxanthine treatment may respond to doxapram,[46,47] which stimulates both the respiratory center and peripheral chemoreceptors. However, the usefulness of doxapram may be limited because of its toxic side effects (including hypertension, central-nervous-system irritability, and seizures) and because of the need for continuous intravenous infusion of the drug.

Blood transfusion to correct anemia and to increase the oxygen-carrying capacity of the blood has been a traditional component of treatment for apnea because it is thought to decrease the potential

for hypoxic respiratory center depression. Conflicting results have come from studies examining breathing-pattern changes in response to transfusions for anemia and other clinical indications. Two studies[48,49] demonstrated decreases in the occurrence of periodic breathing and short apneas following transfusion. In these two studies, no infants had prolonged apneas (> 20 seconds) before or after the transfusions. A third study[50] found no relationship between a wide range of hematocrits (19-64%) and respiratory rate, heart rate, or the incidence of apnea or bradycardia; nor was blood transfusion observed to have a predictable effect on these variables. In view of these conflicting data, the potential benefits and associated risks of transfusion must be weighed carefully for each individual infant.

In some infants with severe or frequent apneic spells, especially very-low-birthweight infants, apnea may persist despite pharmacologic therapy. These infants require mechanical ventilation until they are able to sustain regular breathing.

Persistent Apnea

Although in most infants apneic spells cease by 35-36 weeks postconceptional age, in some infants, especially those born very prematurely, apneic spells persist beyond 37-40 weeks postconceptional age. In these infants, if the incidence of apneic spells cannot adequately be determined using the standard monitors available in the newborn intensive care unit, 12 to 24-hour recordings of impedance pneumography and electrocardiogram (pneumograms) may be indicated. The presence of apnea, bradycardia, or cardiac arrhythmias on pneumogram recordings does not predict the risk of subsequent sudden-infant-death syndrome (SIDS).[51] Also, when pneumograms were obtained in preterm infants prior to hospital discharge, periodic breathing was a common finding, although no relationship was found between long central apneas (> 15 seconds) and any periodic breathing variable.[52] Furthermore, there is no evidence that apnea of prematurity is a risk factor for either apnea of infancy or SIDS.[53]

Infants with persistent apnea should be re-evaluated to determine the etiology; neurologic problems, feeding problems such as reflux, and anatomic causes of airway obstruction should be considered. Reinstitution of theophylline therapy is often useful in infants whose apnea has recurred following discontinuation of theophylline therapy. Infants with persistent apnea who are otherwise ready to be discharged from the hospital may benefit from cardiorespiratory monitoring at home, although few data are available on the effectiveness of home monitoring of infants for this purpose.[53]

Conclusion

Apnea is a disorder of respiratory control that occurs frequently in premature infants and has potentially serious consequences. Improved understanding of the influence that physiologic development exerts on the control of breathing and on disturbances that result in apneic spells will lead to improvements in therapy.

REFERENCES

1. Hiatt IM, Hegyi I, Indyk L, Dangman BC, James LS. Continuous monitoring of P_{O_2} during apnea of prematurity. J Pediatr 1988;98:288-291.
2. Perlman JM, Volpe JJ. Episodes of apnea and bradycardia in the preterm newborn: Impact on the cerebral circulation. Pediatrics 1985;76:333-338.
3. Henderson-Smart DJ. The effect of gestational age on the incidence and duration of recurrent apnea in newborn babies. Aust Paediatr J 1981;17:273-276.
4. Brazy JE, Kinney HC, Oakes WJ. Central nervous system structural lesions causing apnea at birth. J Pediatr 1987;111:163-175.
5. von Euler C. On the central pattern generator for the basic breathing rhythmicity. J Appl Physiol 1983;55:1647-1659.
6. Henderson-Smart W, Pettigrew AG, Campbell W. Clinical apnea and brain-stem neural function in preterm infants. N Engl J Med 1983;308:353-357.
7. Waggener TB, Stark AR, Cohlan BA, Frantz ID. Apnea duration is related to ventilatory oscillation characteristics in newborn infants. J Appl Physiol 1984;57:536-544.
8. Lagercrantz H. Neuromodulators and respiratory control in the infant. Clin Perinatol 1987;14:683-695.
9. Eichenwald EC, Stark AR. Respiratory motor output: Effect of state and maturation in early life. In: Haddad GG, Farber JP, eds. Developmental neurobiology of breathing. New York: Marcel Dekker (in press).
10. Gabriel M, Albani M, Schulte FJ. Apneic spells and sleep states in preterm infants. Pediatrics 1976;57:142-147.
11. Martin RJ, Miller MJ, Carlo WA. Pathogenesis of apnea in preterm infants. J Pediatr 1986;109:733-741.
12. Muller N, Gulston C, Cade D, et al. Diaphragmatic muscle fatigue in the newborn. J Appl Physiol 1979;46:688-695.

13. Heldt GP, Mellroy MB. Distortion of chest wall and work of diaphragm in preterm infants. J Appl Physiol 1987;62:164-169.
14. Stark AR, Cohlan BA, Waggener TB, Frantz ID, Kosch PC. Regulation of end-expiratory lung volume during sleep in premature infants. J Appl Physiol 1987;62:1117-1123.
15. Gerhardt T, Bancalari E. Maturational changes of reflexes influencing respiratory timing in newborns. J Appl Physiol 1981;50:1282-1285.
16. Knill R, Bryan AC. An intercostal-phrenic inhibitory reflex in human newborn infants. J Appl Physiol 1976; 40:352-356.
17. Fox RE, Kosch PC, Feldman HA, Stark AR. Control of inspiratory duration in premature infants. J Appl Physiol 1988;64:2597-2604.
18. Gerhardt T, Bancalari E. Apnea of prematurity: II. Respiratory reflexes. Pediatrics 1984;74:63-66.
19. Dransfield DA, Spitzer AR, Fox WW. Episodic airway obstruction in premature infants. Arch Dis Child 1983;137:441-443.
20. Howell RG, Leszczynski LE, Kosch PC, Stark AR. Uncoupling of laryngeal abduction and inspiratory effort in premature infants (abstract). Pediatr Res 1988;23:510A.
21. Scott SC, Inman JDG, Moss IR. Ontogeny of sleep/wake and cardiorespiratory behavior in unanesthetized piglets. Respir Physiol 1990;80:83-102.
22. Mathew OP, Roberts JL, Thach BT. Pharyngeal airway obstruction in preterm infants during mixed and obstructive apnea. J Pediatr 1982;100:964-968.
23. Thach BT, Stark AR. Spontaneous neck flexion and airway obstruction during apneic spells in preterm infants. J Pediatr 1979;94:275-281.
24. Carlo WA, Miller MJ, Martin RJ. Differential response of respiratory muscles to airway occlusion in infants. J Appl Physiol 1985;59:847-852.
25. Gauda EB, Miller MJ, Carlo WA, Difiore JM, Johnsen DC, Martin RJ. Genioglossus response to airway occlusion in apneic versus non-apneic infants. Pediatr Res 1987;22:683-687.
26. Harned HS, Myracle J, Ferreiro J. Respiratory suppression and swallowing from introduction of fluids into the laryngeal region of the lamb. Pediatr Res 1978;12:1003-1009.
27. Pickens DL, Scheffer G, Thach BT. Prolonged apnea associated with upper airway protective reflexes in apnea of prematurity. Am Rev Respir Dis 1988;137:113-118.
28. Martin RJ, Carlo WA, Robertson SS, Day WR, Bruce EN. Biphasic response of respiratory frequency to hypercapnia in preterm infants. Pediatr Res 1985;19:791-796.
29. Frantz ID, Adler SM, Thach BT, Taeusch HW. Maturational effects on respiratory responses to carbon dioxide in premature infants. J Appl Physiol 1976;41:41-45.
30. Gerhardt T, Bancalari E. Apnea of prematurity: I. Lung function and regulation of breathing. Pediatrics 1984;74:58-62.
31. Rigatto H, Brady JP, de la Torre-Verduzco R. Chemoreceptor reflexes in premature infants: I. The effect of gestational and postnatal age on the ventilatory response to inhalation of 100% and 5% oxygen. Pediatrics 1975;55:604-613.
32. Sankaran K, Wiebe H, Seshia MMK, Boychuck RB, Cates D, Rigatto H. Immediate and late ventilatory response to high and low O_2 in preterm infants and adult subjects. Pediatr Res 1979;13:875-878.
33. Stark AR. Apnea. In: Cloherty JP, Stark AR, eds. Manual of neonatal care. Boston: Little, Brown & Co, 1991:222-226.
34. Warburton D, Stark AR, Taeusch HW. Apnea monitor failure in infants with upper airway obstruction. Pediatrics 1977;60:742-744.
35. Daily W Jr, Klaus M, Meyer HB. Apnea in premature infants: Monitoring, incidence, heart rate changes, and an effect of environmental temperature. Pediatrics 1969;43:510-518.
36. Korner AF, Ruppel EM, Rho JM. Effect of water beds on the sleep and motility of theophylline-treated preterm infants. Pediatrics 1982;70:864-869.
37. Kattwinkel J, Nearman HS, Fanaroff AA, Katona PG, Klaus MH. Apnea of prematurity. J Pediatr 1975;86:588-592.
38. Miller MJ, Carlo WA, Martin RJ. Continuous positive airway pressure selectively reduces obstructive apnea in preterm infants. J Pediatr 1985;106:91-94.
39. Shannon DC, Gotay F, Stein IM, Rogers MC, Todres ID, Moylan FM. Prevention of apnea and bradycardia in low-birth-weight infants. Pediatrics 1975;55:589-594.
40. Aranda JV, Gorman W, Bergsteinson H, Gunn T. Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. J Pediatr 1977;90:467-472.
41. Gerhardt T, McCarthy J, Bancalari E. Effect of aminophylline on respiratory center and reflex activity in premature infants with apnea. Pediatr Res 1983;17:188-191.
42. Davi MJ, Sankaran K, Simons KJ, Simons FE, Seshia MM, Rigatto H. Physiologic changes induced by theophylline in the treatment of apnea in premature infants. J Pediatr 1978;92:91-95.
43. Lagercrantz H, Yamamoto Y, Fredholm BB, Prabhakar NR, von Euler C. Adenosine analogues depress ventilation in rabbit neonates. Theophylline stimulation of respiration via adenosine receptors? Pediatr Res 1984;18:387-390.
44. Aubier M, DeTroyer A, Sampson M, Macklem PT, Roussos C. Aminophylline improves diaphragmatic contractility. N Engl J Med 1981;305:249-252.
45. Gerhardt T, McCarthy J, Bancalari E. Effect of aminophylline on respiratory center activity and metabolic rate in premature infants with idiopathic apnea. Pediatrics 1979;63:537-542.
46. Barrington KJ, Finer NN, Peters KL, Barton J. Physiologic effects of doxapram in idiopathic apnea of prematurity. J Pediatr 1986;108:125-129.
47. Barrington KJ, Finer NN, Torok-Both G, Jamali F, Coutts RT. Dose-response relationship of doxapram in the

therapy for refractory idiopathic apnea of prematurity. Pediatrics 1987;80:79-84.
48. Joshi A, Gerhardt T, Shandloff P, Bancalari E. Blood transfusion effect on the respiratory pattern of preterm infants. Pediatrics 1987;80:79-84.
49. DeMaio JG, Harris MC, Deuber C, Spitzer AR. Effect of blood transfusion on apnea frequency in growing premature infants. J Pediatr 1989;114:1039-1041.
50. Keyes WG, Donohue PK, Spivale JL, Jones MD, Oski FA. Assessing the need for transfusion of premature infants and role of hematocrit, clinical signs, and erythropoietin level. Pediatrics 1989;84:412-417.
51. Southall DP, Richards JM, Rhoden KJ, et al. Prolonged apnea and cardiac arrhythmias in infants discharged from neonatal intensive care units: Failure to predict an increased risk for sudden infant death syndrome. Pediatrics 1982;70:844-851.
52. Glotzbach SF, Baldwin RB, Lederer BA, Tansey PA, Ariagno RL. Periodic breathing in preterm infants: Incidence and characteristics. Pediatrics 1989;84:785-792.
53. Consensus Statement. National Institutes of Health consensus development conference on infantile apnea and home monitoring, September 29 to October 1, 1986. Pediatrics 1987;79:292-299.

Stark Discussion

Jobe: I'm curious about your very last statement. You provide home monitors in some instances. The implication is that what you're really doing is providing monitors for someone with delayed maturation or apnea. How do you decide when to stop the monitoring?

Stark: I think that's an important problem. Our approach, as you've said, is to reserve home monitoring for babies whose breathing stability is delayed, but they're feeding, they're keeping themselves warm, and they're growing. We're just trying to get them home sooner from the hospital. It really requires the right kind of parental environment too. If they are free of apnea at 2 months of age, then we would suggest taking them off the monitor.

O'Rourke: Ann, there's a growing anesthesia literature[1,2] that addresses anesthesia/surgery as potential stimulants for apnea in premature infants. The most commonly studied group are those infants admitted for inguinal hernia repair. Some of these infants with a history of prematurity have been reported to have post-anesthesia apnea up to the age of 60 post-conceptual weeks. These infants require cardiorespiratory monitoring for the first 12-24 postoperative hours. This limits day surgery procedures in post-premature infants less than 52 weeks post-conceptual age or any infant with a history of ongoing apnea.

1. Steward DJ. Preterm infants are more prone to complications following minor surgery than are term infants. Anesthesiology 1982;56:304-306.
2. Kurth CD, Spitzer AR, Broennle AM, Downes JJ. Postoperative apnea in preterm infants. Anesthesiology 1987;66:483-488.

Stark: You are right about that. There is a high incidence of respiratory abnormalities associated with general anesthesia. We recommend spinal anesthesia in those infants, to avoid postoperative apnea.

Mathews: I was interested in the chart you showed that included the EMGs. There's been some adult literature in the last couple of years suggesting that spiking activity (ie, increases in the power frequency spectrum) may be a precursor of muscle fatigue.[1,2] Has anyone followed up on this in infants?

1. Worth H. Electromyography of the respiratory muscles. Prax Klin Pneumol 1988;42:817-819.
2. Repko KD, Greene JG, Enderle JD. A new practical method to detect respiratory muscle fatigue. ISA Trans 1988;paper #88-0204.

Stark: Are you talking about spiking activity in the submental or in another muscle?

Mathews: Sternocleidomastoid.

Stark: The slide that I showed is from Wally's (Carlo) data. He could comment on that also. SM stands for submental, which is where genioglossus muscle is recorded from, and the other EMG is from the diaphragm where electrocardiogram signal contaminates the diaphragm signal.

Mathews: They're using very specialized electrodes and frequency averaging the signals to remove cardiac and background artifact, leaving baseline EMGs from the sternocleidomastoids.

Stark: What they do is look at changes in the EMG frequency spectrum, and there is concern that this may not be as useful as thought initially.

Bowers: According to the news this morning, a study being released today—I didn't catch the name of the journal—shows that the incidence of SIDS is twice as great during the winter compared to other seasons. Does anyone have any comments on that?

Stark: In the SIDS risk-factor study,[1] as opposed to a number of other studies that have been done in the past,[2,3] there was no association with colds. The idea is that inflammation in the already vulnerable upper airway would contribute to apnea. I think that the seasonal influence is thought to be infection related.

1. Hoffman HJ, Damus K, Hillman L, Krongrad E. Risk factors for SIDS. Ann NY Acad Sci 1988;533:13-30.
2. Fedrick J. Sudden unexpected death in infants in the Oxford record linkage area: An analysis with respect to time and place. Br J Prev Soc Med 1973;27:2A-224.
3. Newman NM. The epidemiology of the sudden infant death syndrome in Australia with particular reference to Tasmania, 1975-1981. In: Harper RM, Hoffman HJ, eds. Sudden infant death syndrome: Risk factors and basic mechanisms. New York: PMA Publishing Corp, 1988:53-71.

O'Rourke: Ann, what are your thoughts about the occurrence of apnea in infants with respiratory syncytial virus (RSV) infections?

Stark: That's a difficult question. It's something that has been observed a lot. Whether there is some central influence that is related to the infection or whether it is all an upper-airway-related thing, I don't know. It could also be borderline hypoxemia. Do you have any thoughts on it?

O'Rourke: No specific answers but a few observations. The children who do present with apnea associated with RSV infection usually present prior to the progression of lower-airway disease and hypoxemia. Many are intubated for apnea and then 12 to 48 hours later develop the radiographic and clinical picture of RSV. I've never been able to buy the hypothesis that the apnea was caused by hypoxemia or upper-airway obstruction.

Green: As the evidence against pneumograms has mounted, specifically that they have no predictive value, many places have stopped doing them or are doing fewer. Some centers have started adding other channels to their studies. Would you care to comment on the utility of adding other channels?

Fanaroff: It increases the size of the wallet!

Stark: I think that comment appropriately stands! I know of no studies that indicate in any way that those other channels would increase predictive value.

Green: I think this is an unfortunate area of clinical medicine. We perform studies in great numbers without looking carefully at changes in outcome.

Stark: Right, I agree!

Koff: One study I saw recently was related to smoking and lowered hematocrit.[1] What struck me was something that comes to mind over and over again—a lot of time I think we get caught up in what's going on in our ICU, all of the high-tech things that we have, and sometimes lose sight of the bigger picture, which might be the relationship of what we're coming in with or what these kids are going home to. And I think smoking is one of the issues that sometimes we don't give enough thought to.

1. Bulterys MG, Greenland S, Kraus JF. Chronic fetal hypoxia and sudden infant death syndrome: Interaction between maternal smoking and low hematocrit during pregnancy. Pediatrics 1990;86:535-540.

Stark: Well, I think you're right! We try to make a point of asking parents to avoid smoking and not exposing children—with chronic lung disease, for example—to that kind of a home environment. I think from a public-health standpoint we should do that for everybody.

ECMO: Where Have We Been? Where Are We Going?

P Pearl O'Rourke MD

Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of partial cardiopulmonary bypass (CPB) used for long-term support of respiratory and/or cardiac function. The technology has directly evolved from CPB circuits developed for cardiac surgery. The earliest CPB system used bubble oxygenators, characterized by a direct interface between blood and gas, but these oxygenators caused hemolysis and hence limited prolonged exposure.[1] The development and introduction of membrane oxygenators with a physical separation of the blood and gas phases minimized the problem of hemolysis and made long-term support possible.[2]

In 1972, Hill reported the first successful ECMO support of an adult with acute respiratory failure (ARF).[3] A number of other reports quickly followed.[4,5] Although the overall survival for these patients was low, individual cases were dramatic successes, and ECMO was enthusiastically endorsed in some centers. In response to this enthusiasm, a multicentered study sponsored by the NIH evaluated the benefit of ECMO compared to conventional support of patients with ARF. The results of this study surprised many by demonstrating no difference between the two therapies: Survival with ECMO was 9.5%, survival with conventional therapy 8.3%.[6]

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Although the NIH study essentially terminated the use of ECMO in adults, critics suggested that the study design biased the results by selecting patients with potentially endstage irreversible lung disease. These critics felt that ECMO could be beneficial if applied to patients with reversible disease. Neonates with hypoxemia and hypercarbia secondary to persistent pulmonary hypertension of the newborn (PPHN) were selected as one potential group: ECMO would improve survival if gas exchange could be supported until the pulmonary vascular bed relaxed. The first successful application of neonatal ECMO was reported in 1975 by Bartlett.[7] According to the Registry of the Extracorporeal Life Support Organization (ELSO), 74 neonatal ECMO programs are in operation, with experience in the support of more than 4,000 full-term infants with severe respiratory failure (unpublished report, ELSO Registry, October 1990).

The ECMO Circuit

Most neonatal ECMO is venoarterial (VA) (Fig. 1). A 12- or 14-Fr, multiholed drainage catheter is placed under direct vision into the right internal jugular vein and advanced to the right atrium. Blood flows from the baby by gravity into the ECMO circuit. The first component part of the circuit is a bladder that adds capacitance to the system and provides an access site for sampling and blood and drug administration. From the bladder, blood is pumped into the oxygenator. Occlusive, nonpulsatile rollerhead pumps are most commonly used, although there is a growing experience with centrifugal pumps. A variety of oxygenators are available, but the Sci-Med membrane oxygenator (Life Systems, Plymouth MN) is probably most commonly used. Oxygenators are available in different sizes graded by the amount of blood flow and gas exchange each can accommodate. The oxygenator itself is a silicone envelope wrapped around a hollow spool and fitted into a polyethylene

Abbreviations Used in This Paper

ARDS	— Adult respiratory distress syndrome
ARF	— Acute respiratory failure
CMV	— Conventional mechanical ventilation
CPB	— Cardiopulmonary bypass
$ECCO_2R$	— Extracorporeal carbon dioxide removal
ECMO	— Extracorporeal membrane oxygenation
ELSO	— Extracorporeal Life Support Organization
F_{IO_2}	— Fractional concentration of inspired oxygen
HFOV	— High-frequency oscillatory ventilation
IRV	— Inverse-ratio ventilation
IVH	— Intraventricular hemorrhage
MAP	— Mean airway pressure
MSOF	— Multisystem organ failure
OI	— Oxygenation index
P_{aO_2}	— Partial pressure of arterial oxygen
P_{aCO_2}	— Partial pressure of arterial carbon dioxide
PPHN	— Persistent pulmonary hypertension of the newborn
VA	— Venoarterial
VV	— Venovenous

sleeve. Gas flows in one direction inside the envelope, and blood flows countercurrently (ie, in the opposite direction) on the outside of the envelope. The sweep gas, which delivers oxygen and washes out carbon dioxide (CO_2), is modified to achieve normoxia and normocarbia. The usual oxygen concentration of the sweep gas is between 40% and 60%, and 1-5% carbon dioxide is added to maintain normocarbia. After traversing the oxygenator, blood passes through a heat exchanger and then back into the patient through an 8- to 10-Fr catheter with a single endhole placed in the right common carotid artery and advanced into the ascending aorta. The volume of the circuit may vary slightly, but is in the range of 500-600 mL. The circuit is first primed with crystalloid solution and then with blood that has been corrected for pH and electrolyte concentrations. The entire circuit (and hence the baby) is heparinized to an activated clotting time (ACT) of 210-240 seconds, which is approximately twice normal.

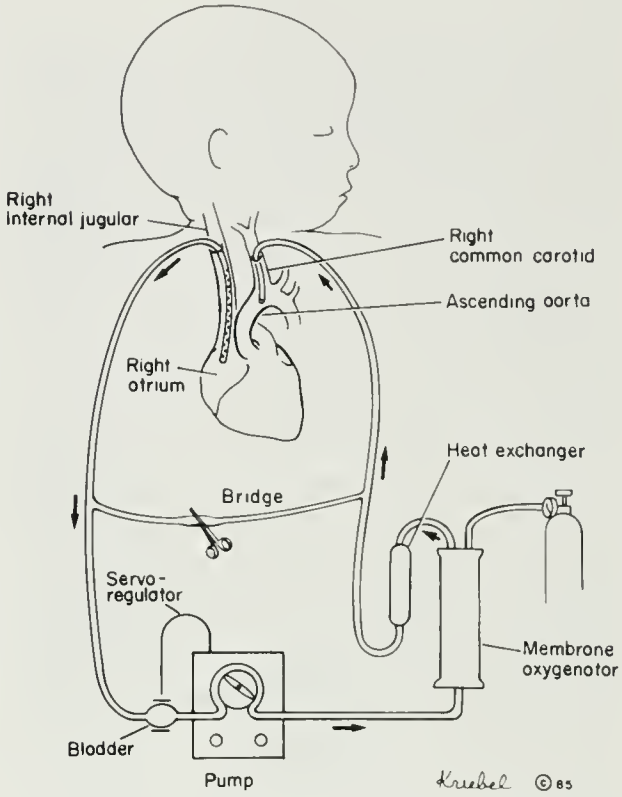

Fig. 1. Diagram showing components of and direction of blood flow in venoarterial ECMO circuit.

The ECMO Process

During the time the infant is on ECMO, the native lungs do not participate in gas exchange. The ventilator is set at 'rest' settings (ie, room air, 4 breaths/min, with a peak inspiratory pressure of 20 cm H_2O and PEEP 5 cm H_2O). The required ECMO flow averages 100 mL/kg/min, which can be 33%-80% of the baby's cardiac output. The flows maintained in any particular baby are chosen to support adequate gas exchange and mean arterial pressure. During ECMO, the goal for P_{aO_2} is 60-100 torr, and for P_{aCO_2} 30-45 torr. Hypocarbia is not attempted.

The duration of ECMO support is a function of the underlying disease. An analysis of ELSO records shows that neonates with meconium aspiration are supported for 3 to 6 days, those with congenital diaphragmatic hernia 7 to 12 days.The decision to wean from ECMO is made when the lung compliance and radiographic status improve. The ECMO flow is slowly decreased while the infant's ability to support gas exchange is tested. When the infant can demonstrate acceptable levels of gas exchange with conventional support, the ECMO catheters are removed, and routine conventional ventilatory support is continued.

Neonatal ECMO Experience

ECMO patient data have been collected since 1981 in a registry based at the University of Michigan and supported by ELSO. Although patient reporting is voluntary, it is estimated that at least 95% of the cases in the U.S. are captured in this registry. As of September 1990, the registry had nearly 4,000 cases (Table 1). These are all neonates who had met institutional criteria for at least 80% predicted mortality. The overall survival for these neonates with ECMO is 83%. Meconium aspiration syndrome is the most common diagnosis and certainly the most successfully treated, with a 93% survival rate. Congenital diaphragmatic hernia has the lowest survival rate (62%) probably as a consequence of the associated pulmonary hypoplasia.[8-10]

Table 1. Cumulative Record of Survival and Demise in Neonates Treated with ECMO, according to the Neonatal ELSO Registry, October 1990

Diagnosis	Survived	Died	Total
Meconium aspiration syndrome	1,468 (93%)	114 (7%)	1,582
Congenital diaphragmatic hernia	444 (61%)	287 (39%)	731
Respiratory distress syndrome	520 (83%)	105 (17%)	625
Persistent pulmonary hypertension of the newborn	487 (87%)	76 (13%)	563
Sepsis or pneumonia	390 (76%)	124 (24%)	514
Other	151 (74%)	54 (26%)	205
TOTAL	3,460 (82%)	760 (18%)	4,220

The general criteria for selecting neonatal patients for ECMO include at least 35 completed weeks of gestation and a predicted mortality of 80% or greater. Infants are excluded if they have a significant pre-existing intraventricular hemorrhage (IVH). Most centers will accept an infant with a Grade 1 IVH; a few centers will accept infants with a Grade 2 IVH. Infants are also excluded if their hypoxemia is secondary to congenital heart disease or if they have other anomalies precluding reasonable survival.

The biggest problem in patient selection has been establishing the validity of indicators for predicted mortality. The criteria used at the present time were formulated from retrospective chart reviews of infants with PPHN.[11-14] The indicators use some measurement of oxygenation. Alveolar-to-arterial oxygen differences, alveolar-to-arterial oxygen ratios, and P_{aO_2}s have been used; however, the oxygenation index (OI) is the most commonly used predictor:

$$OI = \frac{(F_{IO_2})(MAP)}{P_{aO_2}},$$

where MAP is mean airway pressure. An 80% predicted mortality is identified at various centers by an OI ranging from 0.40-0.55. It is important that every center determine which predictor is most accurate in its own institution. Despite best efforts, historical control data provide a number of problems and inaccuracies. Historical data evaluate the care given during the prescribed time, and the data's relevance to current management is questionable. A few studies[15,16] have retrospectively and prospectively evaluated the predicted mortality criteria. Although the criteria were accurate retrospectively, the true mortality determined prospectively was as low as 17% in one study.[16]

The results of these studies obviously raise a number of questions. How much has conventional mechanical ventilation (CMV) changed in the 5 to 7 years since these retrospective reviews were completed? How much institutional difference exists in CMV? The answers to these questions are elusive.

Most ECMO centers used 1981 to 1984 populations as their control group. Although some clinicians state that routine therapy has changed dramatically since that time, others do not appreciate perceptible alterations. The main change that is reported by some is a progression toward 'gentle,' less aggressive ventilator management. The mainstay of conventional management of PPHN has been to maximize pulmonary vasodilation via hyperoxia and induced respiratory and metabolic alkalosis.[17,18] However, this approach carries the physiologic cost of exposing the infant's lungs to 100% oxygen and potentially to elevated airway pressures. Some feel that not only does this approach inflict significant damage to the lungs but also carries no clearly proven benefit.[19,20] These clinicians suggest the use of low airway pressures and low oxygen concentrations to maintain 'just adequate' arterial blood gases: P_{aO_2} 50-60 torr, $P_{aCO_2} < 60$ torr. Wung et al,[21] from Columbia University, have been the most vocal proponents of this gentle therapy. In 1986, they reported 90% survival without the use of ECMO in term neonates with severe respiratory failure. In addition, they also suggest that their method of ventilation results in a much lower incidence of bronchopulmonary dysplasia. Although the numbers reported are small, these reports do dramatically demonstrate the heterogeneity of CMV and the difficulty of inter-institutional comparisons.

In addition to gentle ventilation, high-frequency ventilation is also being used as an adjunct to respiratory management. Carter et al[22] have reported their high-frequency oscillatory ventilation (HFOV) experience in neonates with severe respiratory failure who were referred to their institution for ECMO. These infants were first offered HFOV, and only offered ECMO if they failed to improve with HFOV. Of 46 patients placed on HFOV, 21 survived with HFOV alone and 25 had to be placed on ECMO. Of the 25 placed on ECMO, 22 survived. Carter et al found that infants with pneumonia responded well to HFOV; whereas, infants with meconium aspiration syndrome and sepsis usually failed HFOV and required ECMO. In general, it was thought that infants who had heterogeneous lung disease or cardiovascular compromise as part of their disease did not do well with HFOV. This study is important in that it demonstrates that ECMO does not preclude investigation of other therapies; in fact, it may facilitate clinical trials in this patient population.

Two prospective randomized studies have been designed to overcome the limitations and criticisms of historical control populations and changing CMV. The first by Bartlett et al[23] compared ECMO to conventional management in patients with an 80% predicted mortality. The study design utilized 'play-the-winner' randomization, which resulted in 1 patient's receiving conventional management and 11 ECMO. All ECMO patients survived; the conventionally treated patient died. This study was published in support of ECMO but was accompanied by much criticism.[24]

A second study, by my group,[25] again compared ECMO and conventional therapy. This study used an adaptive design. The first stage of 50:50 randomization was followed by a second non-randomized stage with all patients receiving the 'better' therapy. Of the 10 patients supported conventionally, 6 survived; of the 29 patients who received ECMO, 28 survived. This study supported the efficacy of ECMO, but like the Bartlett study has been criticized for study design.[26,27]

The state of the art for ECMO can be summarized as consisting of a large, successful patient experience compared to historical controls and two well-criticized, prospective, randomized studies. Despite the discussed limitations, ECMO has become standard of care as verified by the growth of ECMO centers and the increase in the number of patients.

ECMO Complications and Risks

The complications and risks of ECMO must also be considered. The obvious risks associated with the procedure are ligation and cannulation of the right common carotid artery and right internal jugular vein, heparinization and exposure to blood products, and risk associated with being sick enough to meet entry criteria. In addition, virtually any procedural catastrophe can occur: An ECMO specialist is at the bedside 24 hours a day to monitor and maintain the circuit in the attempt to minimize these complications.

The primary clinical expression of these technical complications includes infarction and/or hemorrhage. The specific concern is central nervous

system (CNS) injury. Reports from the ELSO registry suggest that 11-30% of ECMO-treated infants suffer some degree of CNS injury that may result in anything from subtle to devastating damage.

The neurologic follow-up is limited to reports from individual institutions. Towne et al[28] published one of the first reports from the early ECMO experience at the University of California-Irvine. Of the 18 patients evaluated at 1 to 14 years, 13 (72%) had normal growth and development, 3 (17%) had moderate neurologic deficit, and 2 (11%) were severely injured. More recent patient experience has been reported from Children's Hospital National Medical Center (CHNMC), the University of Virginia, and the University of Michigan. CHNMC studied 42 consecutive patients[29] with psychomotor tests, cranial ultrasound, and computerized tomography, of whom 25 (59%) had normal neurologic examinations, 9 (21%) were delayed, and 8 (20%) had suspicious results but were not delayed. Krummel and colleagues[30] evaluated 6 patients and reported 5 (83%) normal at 1 to 3 years after ECMO. Andrews et al[31] reported the follow-up of their first 14 survivors, 9 (64%) of whom had normal motor development and 10 (71%) had normal mental ability.

A major problem of neurologic assessment is the fact that the ECMO population is still quite young. It will be important to critically evaluate these children as they mature and reach school age. A second problem of ECMO follow-up is the lack of a control group for comparison. Perhaps the best control group will be those infants referred to as 'near-miss' neonates—those who were referred for ECMO but did not meet ECMO criteria and survived with CMV.

At present, the rate of acute complications is considered acceptable; however, the chronic complication rate requires evaluation.

The Future of ECMO

Where are we going with ECMO? The future of ECMO includes new patient populations and new technology. The goal of technologic advances is to provide safer more effective support, and obviously as ECMO becomes 'safer,' its application will expand.

Virtually any part of the ECMO circuit and procedure deserves critical review. New catheters for VA ECMO, new pumps such as centrifugal pumps, and better heat exchangers are all being evaluated. But, of greatest importance is the development of a venovenous ECMO technique and a heparinless circuit.

Heparinization and clot formation have been considered major risks of ECMO. The best theoretic approach would be to selectively heparinize the circuit and not the baby. At present, the only feasible way to do this is by bonding heparin to the internal surface of the circuit. This has been long discussed and is now being clinically evaluated.[32]

The need to cannulate and ligate the right common carotid artery also introduces major risk. A few centers are attempting carotid repair at the end of the ECMO run to re-establish normal circulation.[33,34] Although this seems appropriate, concern persists about potential complications of stenosis, thrombosis, and embolization after the procedure. Long-term follow-up will be required before carotid repair is generally endorsed.

Venovenous (VV) ECMO provides a different answer. In VV ECMO, blood is drained from and returned to the right side of the circulation. Obviously, this provides only pulmonary support without cardiac support. VV ECMO can be done with either a single- or a double-catheter system. In the double-catheter system, one catheter is used for drainage and the other for return.[35,36] This has been tried in neonates with the outflow catheter placed in the right atrium via the right internal jugular vein and the return catheter in the femoral vein. The right atrium is usually selected for the outflow in order to maximize flows. But, unfortunately, with this system, recirculation occurs when some of the oxygenated blood returned via the femoral vein is captured by the outflow catheter and recirculated through the ECMO circuit.

Various types of single-catheter VV ECMO have been tested. The most promising is a double-lumen catheter that allows continual outflow through a proximal port and inflow through a distal port.[37] Despite the two ports, some recirculation occurs, and the infant is not as well oxygenated as with VA ECMO. Another single-catheter system uses a single-lumen catheter. Similar to dialysis systems,

separate infusion and outflow times are controlled by a tidal flow system.[38,39]

In all types of VV ECMO, the oxygenation cannot be maintained as high as with VA ECMO. The infant's lungs may have to be used to augment gas exchange, which sometimes precludes total lung rest.

An extreme example of VV ECMO is extracorporeal CO_2 removal ($ECCO_2R$). In $ECCO_2R$, oxygenation and ventilation are uncoupled. CO_2 removal (ventilation) is accomplished via VV ECMO using both femoral veins. Because of the solubility and diffusion properties of CO_2, relatively low ECMO flows can maintain a normal CO_2. The native lungs are used for oxygenation. A catheter advanced to the carina provides continuous flow of 100% oxygen. In addition, low-frequency positive-pressure ventilation is delivered. The use of this method has been reported in adult patients by Gattinoni et al from Milan.[40] In their uncontrolled study, 48.8% of patients with a 90% predicted mortality from ARF survived with this therapy. Not enough evidence exists to suggest that $ECCO_2R$ has improved patient survival, but because $ECCO_2R$ does not require arterial cannulation, it certainly is a safer method of support and may well open the door for the earlier use of ECMO in patients with ARF.

Even as these changes in technology are refined, new ECMO populations are being considered.

Premature infants have been identified as one potential group. The only experience[41] with premature infants occurred very early in the history of ECMO, and yielded dismal results secondary to the complications of fatal CNS hemorrhage. However, basic neonatal VA ECMO has improved since this early experience, and some investigators suggest Phase I trials to re-evaluate ECMO in premature infants.

The use of ECMO for non-neonatal pediatric patients is more immediately realistic and has become a rapidly growing field. ECMO is presently being used in some centers in children for pulmonary as well as cardiac support. Each of these indications will be discussed separately.

According to ELSO records (September 1990), approximately 140 pediatric patients have been supported with ECMO for acute respiratory failure with a 42.3% survival rate. These patients differ from neonates in terms of inclusion and exclusion criteria for ECMO. The heterogeneity of patient age, development, and etiologies of disease makes selection more difficult in the pediatric patient.

ARF in the older child is caused by a number of diseases, which, although different, may share some common pulmonary pathophysiology. Unlike PPHN, many of the pediatric diseases are associated with direct air-space diseases with necrotizing alveolitis and deposition of fibrin.[42,43] In addition, most older children are exposed to longer periods of conventional ventilatory support before meeting criteria for CMV failure. As a result, the older child has a much higher probability of iatrogenic injury from elevated airway pressure and/or high oxygen concentrations. In addition, the natural history of various diseases may be different. Although many common final pathways may exist, can injury from hydrocarbon ingestion be compared to injury from viral pneumonia or injury from near-drowning?

Another important issue is the cause of death in older children with ARF—specifically, Is death caused by inadequate gas exchange? Studies of adult patients with adult respiratory distress syndrome (ARDS) show that less than 20% of these patients die from their respiratory failure.[44,45] The majority die from multisystem organ failure (MSOF), and mortality is particularly elevated in the presence of sepsis and/or malignancy. Similar studies in pediatrics are scant, but the existing evidence supports the same conclusion.[46-48] This is in sharp contrast to neonates who succumb to hypoxemia. Therefore, in the older child, can maintenance of gas exchange change the natural history of the disease? Should ECMO be offered earlier—before MSOF occurs? Or, should MSOF be a contraindication for ECMO?

The age of the child may also have an impact on outcome. It is well recognized that the lungs undergo growth and remodeling in the first years of life.[49] These changes are most dramatic in the first months of life, but continue until approximately 6 or 8 years of age. This relative plasticity of the lungs may influence the child's ability to heal. Equivalent injuries to a 10-month-old lung and a 10-year-old lung may have significantly different prognoses. Hence, hard and fast rules for pediatric

patient selection will be exceedingly difficult to formulate. The heterogeneity of the population and the relatively small numbers in any one institution will require a multi-institutional approach.

Concern exists about the use of the carotid artery in the older child. As a result, VV ECMO using both double- and single-catheter systems and $ECCO_2R$ are being evaluated. Identification of the most beneficial and safest ECMO support for the older child requires more experimentation and experience. It is possible that venoarterial cannulation will remain the gold standard but, perhaps, with utilization of a different artery such as the axillary or subclavian.

The risks of ECMO in the older patient are similar to those in the neonate. Although there is anecdotal evidence that the older child has more hemorrhagic complications with pulmonary and cannulation-site bleeding, there appear to be fewer CNS hemorrhagic complications (unpublished report, ELSO Registry, September 1990).

At this time (1991), the state of the art for pediatric pulmonary ECMO is uncertain. While ECMO is being offered more frequently, the paucity of reported data and the lack of comparative studies make patient selection difficult. One prospective, randomized, adult study is in progress. Patients with an 80% predicted mortality are randomized into one of the following three treatment groups: CMV, $ECCO_2R$, or inverse-ratio ventilation (IRV). Preliminary results have failed to demonstrate any differences, and the true mortality has been lower than the predicted mortality in the CMV group.[50] Although it appears that ECMO has a role in the treatment and support of children with ARF, the importance of selecting patients with reversible disease is paramount. No one is interested in repeating the adult experience. We must avoid the risk of prolonging dying.

Interest in VA ECMO for cardiac support has partially emanated from frustration with the use of more routine invasive cardiac-assist devices in the small child.

At present, 190 children have been supported with ECMO for cardiovascular failure, and the survival rate is 43% (unpublished report, ELSO Registry, September 1990). The majority of these children had cardiac dysfunction that was temporally related to corrective surgery for congenital heart disease or transplantation. The selection of these patients requires close involvement of the cardiac surgeon to ascertain the adequacy of anatomic correction or palliation. If children have inoperable disease, they should not be offered ECMO. In a smaller group with failure associated with myocarditis or myocardiopathy, ECMO was used as a bridge to transplantation.

A number of observations of the postoperative experience have been made. Essentially two subpopulations exist depending on when ECMO was offered. Children who were placed on ECMO either in the operating room or within the first 6 hours after surgery have had an extremely high rate of hemorrhage and subsequent mortality.[51,52] Conversely, if the indication for ECMO was progressive cardiovascular failure appearing hours after surgery, a better survival with fewer bleeding complications was seen.[53] This may reflect the fact that those children who require ECMO in the first postoperative hours have more significant myocardial dysfunction or it may emphasize the importance of allowing time for hemostasis prior to systemic heparinization. Some clinicians feel that this experience suggests that ECMO should only be offered to those patients who have some postoperative period of hemostasis.

The exact clinical criteria for cardiac-support ECMO are uncertain. Most centers use a combination of indicators of end-organ perfusion as well as a measure of the level of support. For example, inadequate urine output, elevated bilirubin or prothrombin time, and metabolic acidosis are all used as indicators of inadequate perfusion. The numbers and doses of inotropic and vasoactive drugs required are also considered in conjunction with values of the mean arterial pressure, central-venous pressure, mixed-venous oxygen saturation, and cardiac output.

A number of technical concerns exist with cardiac-support ECMO. Obviously only VA ECMO provides cardiac support. Cannulation sites for VA ECMO have been discussed. The right internal jugular vein and right common carotid artery are most commonly used, but some clinicians feel that better venous drainage can be achieved by direct intrathoracic cannula placement. The main problem

with this approach is that thoracotomy is required for catheter placement and removal and for any intercurrent problems (ie, bleeding or the need for repositioning).[54] A second potential problem is the return of blood to the ascending aorta, which can produce an increased afterload for the left ventricle. Although catheter placement to decompress the left ventricle has been reported,[55] this too would require a thoracotomy.

Summary

ECMO is a relatively young technology that has recently achieved recognition after early clinical disappointment in the late 1970s. At present, it is considered standard therapy for the full-term infant with PPHN who fails CMV, and extraordinary, experimental therapy for older children and adults with ARF and/or cardiac failure.

The ECMO experience in the United States has been characterized by inter-institutional cooperation. From the very beginning, cases have been collected and entered into the National Registry. This registry is now sponsored by the Extracorporeal Life Support Organization (ELSO), which is a consortium of health providers and members of industry who are involved in extracorporeal support. One of the main goals of ELSO is to foster a collegial and cooperative spirit within the ECMO community.[56] This organization fully recognizes the importance and strength of multi-institutional cooperation and participation and realizes that evaluation of any new technology is best done with a multicentered approach.

ECMO is an extremely technical form of support with a number of inherent risks. The growth of ECMO requires ongoing critical assessment as well as constant evaluation of CMV and research for a better understanding of the diseases we attempt to treat.

REFERENCES

1. Kennedi RM, Courey JM, Gaylor DS, Gilchrist T. Artificial organs. Baltimore: University Park Press, 1976:11-19.
2. Clowes GHA, Hopkins AL, Neville WE. An artificial lung dependent upon diffusion of oxygen and carbon dioxide through plastic membranes. J Thorac Surg 1956;32:630-637.
3. Hill JD, O'Brien TG, Murray JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock lung syndrome): Use of the Bramson membrane lung. N Engl J Med 1972;286:629-634.
4. Pierce EC. Is extracorporeal membrane oxygenation a viable technique? Ann Thorac Surg 1981;31:102-104.
5. Short BL, Pearson GD. Neonatal extracorporeal membrane oxygenation: A review. J Intensive Care Med 1986;1:47-63.
6. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe respiratory failure: A randomized prospective study. JAMA 1979;242:2193-2196.
7. Bartlett RH, Gazzaniga AB, Jefferies MR, Huxtable RF, Haidue NH, Fong SW. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. Trans Am Soc Artif Intern Organs 1976;22:80-93.
8. Vacanti JP, Crone RK, Murphy JD, et al. The pulmonary hemodynamic response to perioperative anesthesia in the treatment of high-risk infants with congenital diaphragmatic hernia. J Pediatr Surg 1984;19:672-679.
9. Stolar C, Dillon P, Reyes C. Selective use of extracorporeal membrane oxygenation in the management of congenital diaphragmatic hernia. J Pediatr Surg 1988; 23:207-211.
10. Geggel RL, Murphy JD, Langleben D, Crone RK, Vacanti JP, Reid LM. Congenital diaphragmatic hernia: Arterial structural changes and persistent pulmonary hypertension after surgical repair. J Pediatr 1985;107:457-464.
11. Beck R, Anderson KD, Pearson GD, Cronin J, Miller MK, Short BL. Criteria for extracorporeal membrane oxygenation in a population of infants with persistent pulmonary hypertension of the newborn. J Pediatr Surg 1986;21:297-302.
12. Krummel TM, Greenfield LJ, Kirkpatrick BV, et al. Alveolar-arterial oxygen gradients versus the neonatal pulmonary insufficiency index for prediction of mortality in ECMO candidates. J Pediatr Surg 1984;19:380-384.
13. Marsh TD, Wilkerson SA, Cook LN. Extracorporeal membrane oxygenation selection criteria: Partial pressure of arterial oxygen versus alveolar-arterial oxygen gradient. Pediatrics 1988;82:162-166.
14. Bartlett RH, Gazzaniga AB, Toomasian J, Corwin AG, Roloff D, Rucker R. Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure: 100 cases. Ann Surg 1986;204:236-245.
15. Cole CH, Jillson E, Kessler D. ECMO: Regional evaluation of need and applicability of selection criteria. AJDC 1988;142:1320-1324.
16. Dworetz AR, Moya FR, Sabo B, Gladstone I, Gross I. Survival of infants with persistent pulmonary hypertension without extracorporeal membrane oxygenation. Pediatrics 1989;84:1-6.

17. Fox WW, Doara S. Persistent pulmonary hypertension in the neonate: Diagnosis and management. J Pediatr 1983;103:505-514.
18. Peckham GJ, Fox WW. Physiologic factors affecting pulmonary artery pressure in infants with persistent pulmonary hypertension. J Pediatr 1978;93:1005-1010.
19. Kolobow T, Borelli M, Spatola R. Artificial lung (oxygenators). Artif Organs 1986;10:370-377.
20. Vanhoutte PM. The endothelium-modulators of smooth muscle tone. N Engl J Med 1988;319:512-513.
21. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation without hyperventilation. Pediatrics 1985;76:488-494.
22. Carter JM, Gerstmann DR, Clark RH, et al. High-frequency oscillatory ventilation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. Pediatrics 1990;85:159-164.
23. Bartlett RH, Roloff DW, Cornell RG, Andrews AF, Dillon PW, Zwischenberger JB. Extracorporeal circulation in neonatal respiratory failure: A prospective randomized study. Pediatrics 1985;76:479-487.
24. Ware JH, Epstein MH. Extracorporeal circulation in neonatal respiratory failure: A prospective randomized study (editorial). Pediatrics 1985;76:849-851.
25. O'Rourke PP, Crone RK, Vacanti JP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: A prospective randomized study. Pediatrics 1989;84:957-963.
26. Meinert CL. Extracorporeal membrane oxygenation trials (editorial). Pediatrics 1990;85:365-366.
27. Chalmers TC. A belated randomized control trial (editorial). Pediatrics 1990;85:366-368.
28. Towne BH, Lott IT, Hicks DA, Healey T. Long-term follow-up of infants and children treated with extracorporeal membrane oxygenation (ECMO): A preliminary report. J Pediatr Surg 1985;20:410-414.
29. Glass P, Miller M, Short B. Morbidity for survivors of extracorporeal membrane oxygenation: Neurodevelopment outcome at 1 year of age. Pediatrics 1989;83:72-78.
30. Krummel TM, Greenfield LJ, Kirkpatrick BV, et al. The early evaluation of survivors after extracorporeal membrane oxgenation for neonatal pulmonary failure. J Pediatr Surg 1984;19:585-590.
31. Andrews AF, Nixon CA, Cilley RE, Roloff DW, Bartlett RH. One-to-three-year outcome for 14 neonatal survivors of extracorporeal membrane oxygenation. Pediatrics 1986;78:692-698.
32. Mottaghy K, Oedekoven B, Poppel K, et al. Heparin-free long-term extracorporeal circulation using bioactive surfaces. Trans Am Soc Artif Intern Organs 1989;35:635-637.
33. Spector ML, Wiznitzer M, Walsh-Sukys MC, et al. Carotid reconstruction following ECMO (abstract). Breckenridge CO: 6th Annual Children's Hospital National Medical Center ECMO Symposium, 1990.
34. Crombleholme TM, Adzick NS, deLorimier AA, Longaker MT, Harrison MR. Carotid artery reconstruction following extracorporeal membrane oxygenation. AJDC 1990;144:872-874.
35. Klein MD, Andrews AF, Wesley JR, et al. Venovenous perfusion in ECMO for newborn respiratory insufficiency: A clinical comparison with venoarterial perfusion. Ann Surg 1985;201:520-526.
36. Andrews AF, Klein MD, Toomasian JM, Roloff DW, Bartlett RH. Venovenous extracorporeal membrane oxygenation in neonates with respiratory failure. J Pediatr Surg 1983;18:339-346.
37. Andrews AF, Zwischenberger JB, Cilley RE, Drake KL. Venovenous extracorporeal membrane oxygenation (ECMO) using a double-lumen cannula. Artif Organs 1987;11:265-268.
38. Funakubo A, Fukui Y, Kawamora T. A compact neonatal extracorporeal oxygenator (ECMO) system using a single lumen catheter. Trans Am Soc Artif Organs 1987;33:429-432.
39. Durandy Y, Chevalier JYU, Lecompte Y. Single-cannula venovenous bypass for respiratory membrane lung support. J Thorac Cardiovasc Surg 1990;99:404-409.
40. Gattinoni L, Pesenti A, Mascheroni D, et al. Low frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 1986;256:881-886.
41. White JJ, Andrews HG, Risemberg H, Mazur D, Haller JA. Prolonged respiratory support in newborn infants with a membrane oxygenator. Surgery 1971;70:288-296.
42. Royall JA, Levin DL. Adult respiratory distress syndrome in pediatric patients: I. Clinical aspects, pathophysiology and mechanisms of lung injury. J Pediatr 1988;112:169-180.
43. Royall JA, Levin DL. Adult respiratory distress syndrome in pediatric patients: II. Management. J Pediatr 1988;112:335-347.
44. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with adult respiratory distress syndrome. Am Rev Respir Dis 1985;132:485-489.
45. Bell RC, Coalson JJ, Smith JD, Johanson WG. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983;99:293-298.
46. DeBruin W, Notterman D, Greenwald B. Mortality of ARDS in infants and children. Crit Care Med 1988;17:5111.
47. Holbrook PR, Taylor G, Pollar MM, Fields AL. Adult respiratory distress syndrome in children. Pediatr Clin North Am 1980;2:677-685.
48. Nussbaum E. Adult-type respiratory distress syndrome in children. Clin Chest Med 1987;8:635-639.

49. O'Rourke PP, Crone RK. The respiratory system. In: Gregory GA, ed. Pediatric anesthesia. 2nd ed. New York: Churchill-Livingstone, 1989:63-91.
50. Morris AH, Menlove RL, Rollins RJ, Wallace CJ, Beck E. A controlled clinical trial of a new 3-step therapy that includes extracorporeal CO_2 removal for ARDS. Trans Am Soc Artif Intern Organs 1988;34:48-53.
51. Weinhaus L, Canter C, Noetzel M, et al. Extracorporeal membrane oxygenation for circulatory port after repair of congenital heart defects. Ann Thorac Surg 1989;48:206-212.
52. Redmond CR, Graves ED, Falterman KW, et al. Extracorporeal membrane oxygenation for respiratory and cardiac failure in infants and children. Thorac Cardiovasc Surg 1987;93:199-204.
53. Pennington DG, Swartz MT. Circulatory support in children. Cardiac Surgery: State of the Art Review 1988;3:381-391.
54. Kanter KR, Pennington DG, Weber TR, Zambie MA, Braun P, Martychenko V. Extracorporeal membrane oxygenation for postoperative cardiac support in children. J Thorac Cardiovasc Surg 1987;93:27-35.
55. Eugene J, Ott RA, McColgan SJ, Roohk HV. Vented cardiac assistance: ECMO versus left heart bypass for acute left ventricle failure. Trans Am Soc Artif Intern Organs 1986;32:538-541.
56. Extracorporeal Life Support Organization (ELSO) Charter. October 1989, Ann Arbor, Michigan.

O'Rourke Discussion

Carlo: You have emphasized how difficult it is to predict mortality. It seems to me that studies should be done in which criteria for lower mortality are used.

O'Rourke: The basic difficulty of any further studies is our inability to accurately predict mortality. Having been the "envelope opener" for the Boston randomized study,[1] I was sobered by our lack of ability to prospectively distinguish survivors and nonsurvivors. (There were a few infants who I was certain would die before randomization, these infants were ultimately randomized to conventional therapy and survived.) The problem of inaccurate mortality prediction will be a recurring problem with any future studies unless we allow a conventional therapy arm with no bailout to ECMO, accepting death as one outcome.

1. O'Rourke PP, Crone RK, Vacanti JP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: A prospective randomized study. Pediatrics 1989;84:957-963.

Carlo: Yes, I agree with you it's difficult. We can't just use the historical 80% derived from the work of Short and Pearson and Nicks and Bartlett (using the A-aDO_2 and oxygenation index)[1,2] because neonatal care has improved since then.

1. Short BL, Pearson GD. Neonatal ECMO: A review. J Intensive Care Med 1986;1:47-54.
2. Nicks JJ, Bartlett RH. Extracorporeal membrane oxygenation. In: Carlo WA, Chatburn RL, eds. Neonatal respiratory care. 2nd ed. Chicago: Year Book Medical Publishers, 1988:394-408.

O'Rourke: The Dworetz et al study from Yale used the Short (Washington DC) criteria as well as the oxygenation index; rather than an 80% mortality, they found a true mortality as low as 17%.[1]

1. Dworetz AR, Moya FR, Sabo B, et al. Survival of infants with persistent pulmonary hypertension without extracorporeal membrane oxygenation. Pediatrics 1989;84:1-6.

Carlo: That's right, and that might well be the real mortality.

O'Rourke: In many ways ECMO expands our ability to re-examine our routine support. Conventional care and monitoring have changed dramatically in the past 5 to 10 years. In addition to these advances, it is recognized that there is a lot of institutional bias for conventional care. In short, there is no one acceptable method of caring for these infants. This has recently been demonstrated by the reports from Columbia University where Jen Wung et al[1] have described their "gentle" ventilatory support of infants with PPHN (persistent pulmonary hypertension of the newborn). They avoid the use of muscle relaxants and elevated airway pressures, and do not try to maintain systemic alkalosis and hyperoxia. With this "gentle" approach, the survival rate for PPHN appears to be higher than with the more usual "aggressive" approach to gas exchange. ELSO (Extracorporeal Life Support Organization) has submitted a grant to support a study in which "gentle" and "aggressive" ventilation could be compared: This study would use ECMO as the "bailout" for failures on either limb of this study. This is just one example of how ECMO can hopefully be used to investigate other modes of therapy and support.

1. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation without

hyperventilation. Pediatrics 1985; 76:488-494.

Martin: I would imagine there must be quite a few ways of doing the procedure—is there not a real risk here?

O'Rourke: Yes, there are presently about 76 ECMO centers in the United States and further growth is likely. This growth of ECMO centers must be critically examined, in that there is the potential for too many centers. The reason for this concern is that a minimum number of cases should be done at each center annually in order to maintain the skills of the ECMO team. The exact number of cases is difficult to identify, but ELSO has formulated guidelines for ECMO center criteria and have stated that at least 12 cases per year are needed.

Martin: Even that is not a lot of cases.

O'Rourke: No, I do not think that 12 cases per year is too high. Although this is a suggested guideline, it is impossible to police. There is no licensure for ECMO and no organization willing to accept this responsibility. We are presently discussing this issue with the American Academy of Pediatrics (AAP).

But, we must recognize the pressures that this places on every ECMO team/center. Not only is there the need to maintain skills, but there are also financial issues. An ECMO service is expensive to set up—eg, equipment, training. Most hospital administrators will expect their ECMO programs to be financially accountable and certainly not to lose money. Therefore, the ECMO leadership must decide whether or not the creation of and continuation of a program is medically as well as financially feasible.

Hazinski: Pearl, you and your group are really to be congratulated for demonstrating the effectiveness of this technique. I want to disagree with Wally (Carlo) a little bit. I think you can't study ECMO in truly randomized trials, but ECMO ought to be used as the "rescue therapy" for patients who fail maximum medical therapy. Randomized trials must be performed, however, to figure out the proper therapy for neonatal hypoxic respiratory failure. I think it's a mistake to cross them over, and I think we made a mistake on the HIFI trial.[1] We thought it was the ethical thing to do when in fact it turned out to confound the results. But, anyway, I wanted to ask you this. In your study[2] you withheld information from the parents that in fact their infants were participating in a randomized trial. As I understand it, you randomized them and then you went to the parents to get consent for only one treatment. You never mentioned the fact that they had been randomized—so that you were put in the position of not having to mention the null hypothesis or the uncertainty of the efficacy of the intervention.

1. Rigatto H, Davi M, Frantz ID III, et al. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 1989;320:88-93.
2. O'Rourke PP, Crone RK, Vacanti JP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: A prospective randomized study. Pediatrics 1989;84:957-963.

O'Rourke: Yes, we used the Zelen approach[1] in which you randomize prior to seeking consent. The group that is continued on routine therapy does not know that they are in a study, and consent is only obtained from the group receiving the experimental therapy. This approach has been used in previous studies and was accepted by our IRBs (institutional review boards) after many hours of discussion and soul searching. Despite these discussions, the study has been severely criticized in both medical and lay press.

Aside from the issue of getting consent, there is a major problem with any study that allows death as an endpoint without a bailout clause. This is only possible if there is institutional equipoise regarding the two therapies proposed—this means that you simply do not know which is the better therapy. If there is institutional equipoise, but a lack of personal equipoise, then this becomes problematic for the members of the study group.

Although most ECMO programs are started as clinical programs, there is a lot of interest in using ECMO as a research tool. In fact, ECMO research has improved markedly in the past five years.

I think most ECMO programs are started with the premise that neonatal ECMO will be replaced by the discovery of the perfect specific pulmonary vasodilator. We should use our experience with ECMO to better study and understand the basic pathophysiology that is occurring in these infants. Hence, for obvious reasons the pulmonary vascular bed is of utmost interest. In addition there is research aimed at better understanding the physiologic cost of ECMO in terms of the loss of pulsatile flow and perfusion to the brain and and coronaries.

1. Zelen M. A new design for randomized clinical trials. N Engl J Med 1979;300:1242-1245.

Carlo: I want to strongly disagree with Tom's (Hazinski) comments. I think there is a lot of room for very-well-designed studies. We might be starting ECMO too late. Maybe we should start doing ECMO earlier. The only way we are going to find out is if we design good studies that answer these questions. But, I strongly disagree with Tom's comments, and we do not have to let

patients die if we do such a study. That doesn't have to be the outcome of conventional therapy.

Rodriguez: What do you think is the role of the respiratory care practitioner in the administration of ECMO?

O'Rourke: Most programs are run with RNs, but they can be run with any medically trained personnel who understand cardiopulmonary perfusion, gas exchange, and equipment. When I was in Boston, we started our program exclusively using RCPs, and in Seattle we have a combined program with RNs and RCPs. There are advantages to combining the two specialties—each brings a different expertise. Nursing as a rule is quite focused on guidelines and protocols, which are absolutely necessary for a safe and successful program. Nursing also adds the knowledge of total patient care. RCPs generally have more mechanical expertise and have an easy time interfacing with the circuit. In addition, in my experience, RCPs tend to be a bit more "cowboy," which can add new creative innovations. In short, I think that the best team includes both RNs and RCPs.

Despite my thoughts, RCPs doing ECMO are a true minority. This organization should support the ECMO-RCP population and work toward formal liaison with ELSO.

Fanaroff: Just to fill in on the reconstruction that was started by our thoracic surgeon, Mike Spector—criteria for reconstruction: no hemorrhage at site of the insertion of the catheter and no signs of infection. They've done about 25 now with follow-up magnetic resonance angiography. This has shown that the vessels are intact, there's re-establishment of circulation, and there's no evidence of infarction on the side of the reanastomosis. There's only one vessel that shows stenosis (and that stenosis was present from early on). So, I think this has been very encouraging. I'd like to also add my plea to that of Tom Hazinski that there be more basic science studies carried out on ECMO. And I think with the lung at rest, that we should be doing a lot more investigation of the biochemistry of lung injury.

Salyer: I have two short questions: (1) What do you think the minimal educational requirements should be for respiratory therapists participating in ECMO? (2) Could you speak briefly about the costs of the training?

O'Rourke: ELSO is completing training modules and trying to provide some idea of the amount of study, laboratory, and bedside experience that's necessary, from which we can estimate training costs.

Salyer: Do you have certified respiratory therapy technicians in your ECMO program?

O'Rourke: Yes. In terms of treatment costs—the cost varies tremendously by center. Most centers charge separately for surgical costs and physician costs. Ignoring physician costs, the cost to run an ECMO is in the range of $1,000 to $2,400 per day. ECMO in many places has been found to be cheaper than conventional therapy because the ECMO infants may wean from mechanical ventilation earlier.

The Role of Surfactant Therapy in Neonatal Respiratory Distress

Alan H Jobe MD PhD

Rationale for Surfactant Administration

Physiologic Abnormalities in RDS

Infants with respiratory distress syndrome (RDS) have an increased work of breathing because of their attempts to inflate atelectatic and stiff lungs (decreased compliance) to maintain adequate P_{O_2} and acceptable P_{CO_2} levels.[1] Long, gasping efforts and high-pressure inspiratory efforts result in small tidal volumes. At the same time, the lungs empty rapidly to lung volumes below a physiologic functional residual capacity (FRC). The atelectasis contributes to increased pulmonary vascular resistance that promotes or aggravates right-to-left shunt. The result is severe hypoxia that can be corrected only partly by increasing the oxygen content of the inspired gases.

These physiologic abnormalities are accompanied by a number of pathologic findings that reveal how the preterm surfactant-deficient lung is injured as a result of either spontaneous or mechanical ventilation. The lungs of infants who died of RDS soon after birth in the era before the advent of mechanical ventilators had severe atelectasis of alveolar units with the development of bronchiolar epithelial disruptions after just a short period of spontaneous breathing. This bronchiolar epithelial damage has been termed "bronchiolar epithelial lesions" by Robertson.[2] With mechanical ventilation and more prolonged survival, hyaline membranes and alveolar edema became more prominent as did marked distortion and dilation of distal airways. The hallmarks of lung injury in RDS lungs then are atelectasis, small airway epithelial damage, and pulmonary edema.[2] Now that surfactant treatments for infants with RDS are available, it is useful to examine the experimental and clinical results with surfactant treatments to see how effectively such treatments can reverse the major physiologic and pathologic abnormalities in RDS.

Surfactant Pool Size and Function

Measurements of alveolar surfactant-pool size in infants with RDS, are similar to values reported for animal models of RDS[3-5] (Table 1). Infants with RDS have much less surfactant than do term animals. In preterm animals, the quantity of surfactant correlates directly with the severity of the respiratory failure;[6,7] yet, in animals with moderate respiratory failure, the size of the surfactant pool is similar to the size of the pool found in the adult when expressed as quantity per kilogram of body weight. The explanation for this paradox is in the abnormal function of surfactant within the preterm lung.

Samples of air-space liquid from infants with RDS have abnormal surface properties when tested in vitro. However, surfactant with good function can be recovered from such samples by a simple centrifugation procedure that separates the large surface-active aggregates from soluble inactivators in the air-space liquid.[8] No evidence suggests that surfactant in the preterm infant is functionally abnormal relative to that of the adult if inhibitory activity is removed. This issue of abnormal surfactant

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Abbreviations Used in This Paper

BPD — Bronchopulmonary dysplasia
FRC — Functional residual capacity
P_{O_2} — Partial pressure of oxygen
P_{CO_2} — Partial pressure of carbon dioxide
PIP — Peak inspiratory pressure
RDS — Respiratory distress syndrome
F_{IO_2} — Fractional concentration of inspired oxygen

function is critical to an understanding of the lung abnormalities of infants with RDS in relation to surfactant treatments. Surfactant inactivation is caused primarily by interference with the development of surfactant monolayers by soluble proteins.[9,10] The inactivation is a reversible biophysical phenomenon that does not break down surfactant lipids or protein. The inactivation is a strongly dose-dependent phenomenon, with the proteins having little effect if large amounts of surfactant are present. However, severe protein inactivation can result if only small amounts of surfactant are present in the alveoli. Different amounts of inactivation occur depending on the protein species or type of surfactant present in the air spaces. Surfactant inactivation is a major problem in RDS because surfactant pool sizes are low and the air spaces tend to fill with protein-rich liquid.[8] Jackson and his colleagues[11] have demonstrated that the reduced total lung capacity in preterm monkeys with RDS at 3 hours of age results primarily from interstitial edema and alveolar filling with proteinaceous liquid rather than from atelectasis.

Table 1. Representative Alveolar Surfactant Pool Sizes in Four Species

	Mg Surfactant/kg Body Weight		
Species	Ventilated Preterm with RDS	Term Newborn	Adult
Sheep	12	120	Adult
Monkey	6	100	13
Rabbit	<4	50	12
Man	3.4*;8	—	4

*Infants who died of RDS without mechanical ventilation
Table modified from Reference 5.

Based on measurements in animals, the lungs of the preterm subject tend to leak protein in the immediate newborn period, an abnormality that can be aggravated by barotrauma and lung injury.[12] This tendency of the preterm lung to leak is inversely related to gestational age, indicating that the abnormality is a maturation-dependent variable that is independent of surfactant maturation.[13] For example, the protein leak can be decreased in animal models by maternal corticosteroid treatments.[14]

Effects of Surfactant Treatments on Surfactant Pool Size and Function

Most experimental and clinical protocols empirically have used surfactant doses of about 100 mg surfactant/kg body weight.[5] This is a dose that is about 10-fold in excess of the amount of surfactant present in the healthy adult lung (Table 1). However, much of the surfactant that is delivered to the lungs via the airways cannot be recovered from the air spaces by saline lavage even shortly after treatment.[15] This lung association (or apparent loss from the air spaces) is presumed to represent uptake of the surfactant by the lung into metabolic pathways for reprocessing and resecretion.[16] For example, we found only about 20% of the treatment dose of surfactant was recoverable from the air spaces of preterm lambs 24 hours after treatment.[17] The result is that much of the treatment dose is not functioning in the air spaces. This loss of surfactant is from the air spaces to the lung tissue but not from the lung because almost no catabolism of surfactant appears to occur in the preterm or term lung.[17]

Surfactant treatments are given clinically either as single or divided intratracheal boluses in saline, with the infant positioned to try to optimize distribution or by multiple small instillations timed with inspiration. These techniques have not been compared for their effect on distribution of surfactant at either the lobar or alveolar levels. Although suspension of surfactant in the liquid-filled fetal lung (before the first breath) followed by ventilation does result in a more uniform distribution than bolus instillation into aerated lungs, neither technique gives very uniform distribution.[18] The variables likely to impact surfactant distribution are

the volume administered (the larger the volume, the better the distribution), the viscosity of the surfactant, the homogeneity of the lung disease (surfactant preferentially enters ventilated rather than atelectatic or liquid-filled lung), the style of mechanical ventilation during treatment, and the position of the patient. The dose of surfactant used for treatment clinically is high—in part to overcome the inhomogeneity of distribution.

Surfactant treatments certainly do increase alveolar pool size, but the effects of tissue uptake and nonuniform distribution mean that the doses of exogenous surfactant needed to reproduce the effects of spontaneous increases in the endogenous pools with lung maturation are quite different (Fig. 1). Compliances improved in preterm rabbits as endogenous surfactant pools increased or as treatment doses of natural rabbit surfactant increased, but about 10-fold more treatment surfactant was needed to achieve the effect.[7,19]

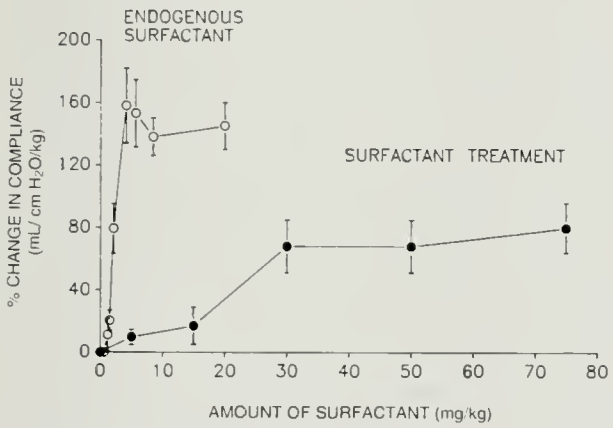

Fig. 1. Comparison of compliances in preterm rabbits following the administration of endogenous (○) and exogenous (●) surfactant. The compliance relationship for the endogenous pool was determined by measuring compliances in 27- and 28-day-gestation, preterm, ventilated rabbits and then lavaging the lung to measure alveolar surfactant pools.[7] This curve includes the effects of both spontaneous increases in surfactant and lung maturation. The curve for the change in compliances with treatment with different doses of rabbit natural surfactant was generated using immature 27-day-gestation, preterm rabbits.[19] The larger maximal compliance change in the curve for the endogenous pool probably reflects the combined effects of increasing surfactant pools and maturation of lung structure. Figure redrawn from data in References 7 and 19.

Surfactant treatments also should improve lung function by overcoming the inactivation caused by the soluble proteins in the air spaces and/or by decreasing the movement of these proteins into the lungs. Such treatments do improve the surface properties of samples taken from the lungs of preterm ventilated animals for periods up to 24 hours after a single treatment.[17] Surfactant can also sharply decrease the movement of plasma proteins to the air spaces as measured in preterm rabbits and sheep[12,20] (Fig. 2), and can effectively prevent the development of bronchiolar epithelial lesions and hyaline membranes, the overt signs of lung injury in RDS.[21] Airway samples from infants who were treated with surfactant contained less elastase and more α-1 protease inhibitor than did samples from RDS infants without surfactant treatment, a clinical finding consistent with a decrease in lung injury following surfactant treatments.[22]

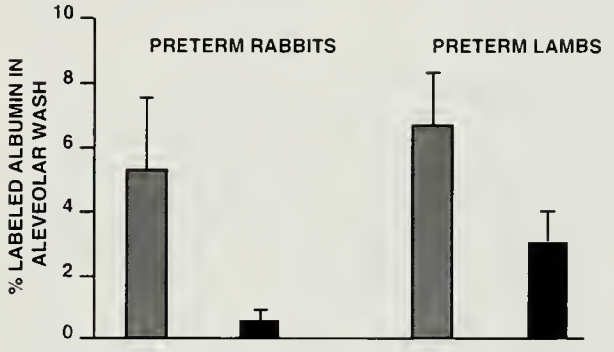

Fig. 2. Effects of surfactant on the leak of labeled intravascular albumin into the air spaces of preterm ventilated animals. ▭ = no surfactant treatment; ■ = surfactant treated. Preterm rabbits and sheep were delivered and ventilated following the intravascular injection of radiolabeled albumin. Natural calf surfactant (50 mg/kg) was used to treat 27-day-gestation rabbits, and the 135-day-gestation lambs were treated with 50 mg/kg of natural sheep surfactant. The recovery of labeled albumin in alveolar washes as percent of injected dose was measured at 30 min of age in the rabbits and at 3 h of age in the lambs. Surfactant significantly decreased labeled-albumin recovery in both species.[12,20]

Physiologic Responses to Surfactant

The most generally reported response of infants with RDS to surfactant treatment is an improve-

ment in oxygenation, with a modest and less rapid decrease in respiratory-support variables.[5] This response is consistent with responses noted in preterm lambs and baboons under controlled experimental conditions.[23,24] Oxygenation can improve almost instantly whereas improvements in P_{CO_2} values, compliances, and, therefore, ventilatory-support variables change more gradually. Why oxygenation improves without compliance changes has been the subject of considerable discussion.[25,26] The explanation for the inconsistency almost certainly results from acute changes in lung volumes following surfactant treatments.[27]

The effect of surfactant on lung volumes can be seen clearly from static pressure-volume curves (Fig. 3). Maximal lung volumes are increased 2.5-fold, and volumes at low pressures on deflation are greatly increased over control values with surfactant treatment of preterm rabbits. These volume changes mean that all the pressure-volume relationships of the lungs are altered. Compliance measurements are a function of the lung volumes across which they are measured. It is apparent by clinical observation that some infants have an acute increase in FRC following surfactant treatment. Therefore, the rapid improvement in oxygenation results from reversal of atelectasis and the tendency of the lung to collapse at end-expiration. Lung mechanics also are altered by surfactant treatment.[28,29] Time constants for inflation decrease; whereas time constants for deflation increase, resulting in less effective lung emptying and high FRCs because of gas trapping if rapid respiratory rates or high positive end-expiratory pressures are used. Davis et al[25] found compliance changes following surfactant treatments only with spontaneous ventilation and not with mechanical breaths. My impression is that in some infants P_{CO_2} values do not fall and compliance changes are not noted because ventilator settings are not turned down in response to a clinical assessment of lung volumes.

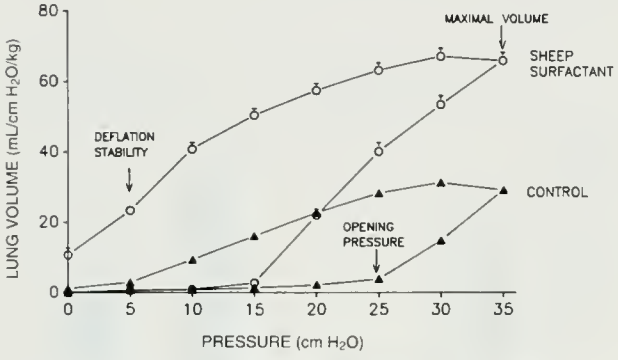

Fig. 3. Effects of natural sheep surfactant on the quasi-static pressure-volume relationships of 27-day-gestation, preterm rabbit lungs. The rabbits were treated with 50 mg/kg of surfactant or nothing (control) and ventilated for a short period after which the pressure-volume-curve measurements were made. Surfactant treatments decreased the pressure required to open the lungs on inflation from about 25 cm H_2O pressure to 15 cm H_2O, increased lung volumes at maximal pressures of 35 cm H_2O, and improved deflation stability at low transpulmonary pressures.

Clinical Results

Perspective on the Clinical Trials

The first clinical trial reported by Fujiwara et al[30] in 1980 was based on the series of demonstrations by Enhorning and Robertson and their colleagues[31] from 1972 to 1978, showing that surfactant treatments could improve lung expansion and prolong survival of preterm rabbits. The rapid development of bronchiolar epithelial lesions and lung damage in preterm rabbits led to the concept that surfactant treatments would not be effective unless given at birth and before much ventilation had occurred.[31] However, in Fujiwara's initial trial[30] 10 infants with severe RDS (mean P_{CO_2}, 50 torr; mean pH, 7.13; average peak inspiratory pressure (PIP), 30 cm H_2O; mean F_{IO_2}, 0.81) were treated with a calf-lung surfactant at a mean age of 12 hours. All infants exhibited improved oxygenation (mean F_{IO_2} decreased to about 0.4 within 3 hours), and PIPs had decreased to 22 cm H_2O 6 hours after treatment. Thus, infants will respond to surfactant even if it is given after the initiation of mechanical ventilation.

To evaluate the timing of treatment, subsequent randomized trials have taken two primary forms—treatment in the delivery room within the first few minutes of birth and treatment of infants with RDS after initial stabilization, generally between about 2 and 8 hours of age.[32] The most recent trials have

used multiple-dose protocols and direct comparisons of delivery room treatment versus treatment of established RDS. Unfortunately most of these multiple-dose trials, which are the most impressive in terms of demonstrating decreased mortality and/or bronchopulmonary dysplasia (BPD), were not published at the time this review was written, although some of the results were available in product monographs and as abstracts.[33,34] I have summarized the clinical trials by focusing only on the published, randomized, controlled trials, with brief comments about the unpublished information.

Any discussion of surfactant-treatment responses is complicated by the multiple sources and types of surfactant that have been used. The surfactants that have been evaluated clinically fall into two general categories, surfactants derived from mammalian sources and surfactants made from synthetic lipid mixtures. The nomenclature throughout the literature is not consistent. I will call natural surfactant that material recovered from alveolar lavage liquid, whereas modified natural surfactant is the species-homologous or -heterologous material prepared by processing of surfactant from natural sources (generally by lipid-solvent-extraction procedures, with removal or addition of specific components). An artificial surfactant is a mixture of synthetic compounds that may or may not be components of natural surfactant. The initial randomized trials were single-dose trials with the exception of the trials with surfactant from human amniotic liquid in which some infants received extra doses.[35,36] Subsequent trials (mostly unpublished) include multiple-dose protocols to achieve several goals—an increase in the percent of infants who respond, an increased duration of the response, and a decreased incidence of BPD.[37,38]

Delivery-Room Treatments—Modified Natural Surfactants

Five published trials report the treatment of infants at an aggregate mean gestational age of 27 weeks and mean birthweight of 970 g (Table 2).[36,39-42] In all trials, the treated infants required less supplemental oxygen and less ventilatory support than did control infants. The trials of delivery-room treatment were designed to be 'prevention' treatments or 'prophylactic' treatments that did decrease the incidence of RDS. For example, in the Enhorning trial[39] the clinical diagnosis of RDS was made in 37% of treated infants versus 70% of control infants, and the overall severity of RDS was decreased. However, surfactant treatments did not prevent RDS. This is an important point to recognize: Surfactant is not a panacea; rather, it decreases the incidence and severity of RDS but does not eliminate the clinical diagnosis. The air leak complications of RDS are strikingly de-creased, but no clear effect on the incidence of BPD has been seen. In contrast, surfactant treatments have not altered the incidences of other complications of prematurity. Across the 5 trials, death was decreased by about 50%. On average about 70% of infants weighing 1 kg can be expected to develop RDS, and most delivery-room treatment protocols do not try to eliminate the 30% of infants not at risk for RDS. Therefore, a criticism of this treatment strategy is that some infants are treated unnecessarily.[36]

Table 2. Results of Treatment with Surfactant Immediately following Birth, from 5 Randomized Studies[36,39-42] including 384 Patients*

Complications of RDS	Surfactant	Control
Pneumothorax	8.2%	19.0%
PIE†	9.6%	36.7%
BPD	29.7%	36.8%
Complications of prematurity		
PDA	40.7%	37.9%
Grade III & IV IVH	12.9%	13.7%
Necrotizing enterocolitis	7.7%	4.7%
Death	11.3%	21.1%

* Average gestational age = 27.2 weeks and average weight = 970 g.

† PIE = pulmonary interstitial emphysema; BPD = bronchopulmonary dysplasia; PDA = patent ductus arteriosus; and IVH = intraventricular hemorrhage.

A multidose strategy was used in a multicenter trial for infants weighing between 600 and 1250 g.[34] The infants were randomized to Survanta® (Ross Laboratories, Columbus OH), a surfactant prepared from bovine lung, (n = 119) or air placebo

(n = 124) and received a treatment in the delivery room. Infants could receive up to 3 additional treatments over the first 48 hours of life for persistent respiratory problems. A preliminary analysis indicated that the multidose strategy decreased deaths due to any cause from 23% in the air controls to 8% in the Survanta-treated infants, although the incidence of BPD in survivors was not decreased. This trial again emphasized that even multiple surfactant treatments do not prevent RDS because 66% of treated infants had respiratory symptoms versus 89% of air-control infants. Nevertheless, air leaks and death were remarkably decreased in this group of very tiny infants.

Treatment of Established RDS–Modified Natural Surfactants

Seven randomized controlled trials of the treatment of RDS with animal-source surfactants have been reported for infants at a mean gestational age of 28.6 weeks and a mean birthweight of 1200 g (Table 3).[35,37,43-47] The infants required about 85% oxygen and mean airway pressures of about 12 cm H_2O at the time of treatment. Oxygen requirements were decreased by the surfactant treatments with modest-to-no initial effects on mean airway pressures. Despite the lack of clear impact on ventilatory settings, the air-leak complications of RDS were decreased, as was death rate (in the aggregate) across studies. As with delivery-room treatments, surfactant treatment had no impact on the complications of prematurity. Dunn et al[37] reported that multiple doses of surfactant sustained the improvement in oxygenation relative to a single dose, although the multiple doses did not decrease time of intubation. The advantage of this strategy for treating RDS is that only infants requiring treatment are exposed to surfactant.

Table 3. Summary of Results of Surfactant Treatments of Established RDS from 7 Randomized Studies[35,37,43-47] including 556 Patients*

	Surfactant	Control
Complications of RDS		
Pneumothorax	16.2%	39.6%
PIE†	14.1%	34.0%
BPD	23.7%	29.1%
Complications of prematurity		
PDA	54.3%	51.3%
Grade 3 & 4 IVH	18.9%	22.6%
Necrotizing enterocolitis	5.2%	5.7%
Death	19.2%	31.3%

* Average gestational age = 28.6 weeks, average weight = 1200 g, age at treatment = 6 h; some infants in treatment group received more than 1 dose of surfactant.

† PIE = pulmonary interstitial emphysema; BPD = bronchopulmonary dysplasia; PDA = patent ductus arteriosus; and IVH = intraventricular hemorrhage.

Artificial Surfactants

Artificial surfactants are inherently attractive for the treatment of RDS because of their known compositions and lack of protein. A mixture of dipalmitoylphosphatidylcholine and phosphatidylglycerol (7:3) has been extensively evaluated in England in multidose protocols of 328 infants beginning immediately after birth.[48] Treatments of infants at a mean gestational age of 27.6 weeks and birthweight of 1080 g resulted in a striking decrease in overall mortality from 27% to 14%. This surfactant seemed to have less impact on the incidence of air leaks and did not alter the incidence of chronic lung disease. The surfactant was particularly effective in infants of less than 29-weeks gestational age in whom intraventricular hemorrhage decreased.

The artificial surfactant evaluated in this country and Canada is a mixture of dipalmitoylphosphatidylcholine, hexadecanol (the 16-carbon-chain alcohol), and tyloxapol (an emulsifying agent) and is called Exosurf® (Burroughs Wellcome, Research Triangle Park NC).[33] Results with a single delivery-room dose of Exosurf to infants in the 700-1100 g birthweight range decreased overall mortality from 30% to 20% and decreased pneumothorax from 19% to 11% without decreasing the incidence of BPD.[33] Two doses of Exosurf given after the onset of RDS for infants with birthweights between 700 and 1350 g decreased overall mortality from 27% to 15%, but again no decrease in BPD was seen among survivors, although both pneumothorax and pulmonary interstitial emphysema decreased.[33] Although most studies of sur-

factant efficacy have concentrated on very tiny infants, Exosurf was evaluated in a 2-dose protocol in more than 600 infants with RDS with birthweights over 1250 g.[33] Despite low overall mortality rates, Exosurf decreased death from RDS from 3% to 1%, decreased BPD from 5.7% to 2.7%, and decreased air-leak complications as well. This trial demonstrated clear benefits of treatments for larger infants at less risk of death and complications from RDS.

Choosing a Surfactant

Although it is now clear that both modified natural surfactants and artificial surfactants can alter the clinical course of RDS, the responses to the various surfactants probably are not equivalent. Most trials have used a surfactant dose of about 100 mg/kg for either single or multiple-dose protocols. The trials with human amniotic-fluid surfactant have used a dose of about 60 mg/kg,[35,36] whereas a beef-lung-extract surfactant tested in Europe was used at a dose of 200 mg/kg.[45] A randomized trial in Japan[49] found that a surfactant dose of 120 mg/kg decreased oxygen needs and decreased both intraventricular hemorrhage and BPD in comparison to a group of infants receiving 60 mg/kg surfactant. A dose of 100 mg/kg is reasonable based on the empiric results of the trials, but it is not clear that different surfactants have similar dose-response curves. Direct comparisons of published trials with different surfactants are risky because patient-selection criteria and dose timing vary as do infant populations. The most important outcome variables are death and BPD, and differences in these variables versus controls were demonstrated convincingly only in large studies. Impractically large studies would be needed to compare two effective surfactants for differences in death and BPD. Short-term differences in ventilatory variables could be tested and probably would show differences.

Why Surfactant Does Not Always Work

My interpretation of the clinical data is that about 50% of surfactant-treated infants have dramatic and sustained responses, about 25% of treated infants have improvements in the lung disease, and little effect is seen in about 25% of infants. If we assume good surfactants and good treatment techniques, this means that about 50% of the infants now classified as having RDS have surfactant deficiency as the primary problem while the other infants have other lung problems that may or may not include surfactant deficiency. The challenge for the future is to better understand the lung diseases in those infants thought to have RDS that do not improve with surfactant treatments. The surfactant treatment can be the diagnostic tool used to distinguish between infants with primary surfactant deficiency and those with other primary problems.[50]

The major reason that infants with the clinical diagnosis of RDS do not respond to surfactant is that these infants have other lung problems related to lung development or other diseases such as pneumonia. In general, most preterm infants have some degree of induced lung maturation resulting from the abnormalities that precipitated the preterm delivery.[50] The maturation of the surfactant system need not occur in parallel with other important maturational events such as the development of airway structural support, epithelial and endothelial barriers, and liquid-clearance mechanisms. Severe pulmonary interstitial emphysema and pulmonary edema are characteristic of the very immature lung. Although surfactant treatments may mitigate these problems, it cannot prevent them in the very immature lung.[20]

In recent years, mild degrees of pulmonary hypoplasia have been described in preterm infants with prolonged rupture of membranes.[51] While lethal pulmonary hypoplasia is at one end of the spectrum, the milder forms generally are classified as RDS.[52] These infants would not be expected to respond very well to surfactant because of the inadequacy of the gas exchange surface. Alveolarization also seems to occur to different degrees in different infants.[53] By analogy, infants without frank pulmonary hypoplasia but with fewer alveoli should respond less dramatically to surfactant than those with more alveoli. The different timing of and abnormalities in maturation of lung structure affect surfactant responses.

Other diseases such as congenital pneumonia and Group-B streptococcus sepsis or pneumonia

syndromes may also present as RDS. These lung diseases may occur in infants with surfactant deficiency, or surfactant deficiency may be a secondary problem because of the pulmonary edema. While the infants may respond to a surfactant treatment, the response may not be large or sustained. A concern is that surfactant used for treatment could blunt the immune host-defense response of the infected infant;[54] however, this problem has not been evident in the clinical trials to date.

A number of cautionary notes are in order in terms of the techniques used to treat infants with surfactant. The surfactants are given by tracheal injection as single or divided boluses or by repetitive small additions during inspiration. In general, the larger the volume administered, the better the distribution is likely to be, but large volumes can cause an acute decrease in gas exchange by occluding large and small airways with the surfactant suspension. This problem is more severe in infants with very mild disease because lower ventilator pressures do not effectively push the surfactant distally into the lungs. Transient increases in ventilatory pressures may be needed to rapidly distribute the surfactant from the airways to the respiratory units.

A number of poorly characterized variables of clinical care may alter clinical response. In the multicenter trials, some institutions have had very good success with surfactant while others have had less success. I suspect that ventilatory strategies may be important to responses. Fujiwara et al[55] believe that ventilation with rapid rates and small tidal-volumes may result in more initial airway obstruction and inadequate distribution of the surfactant, whereas inadvertent positive end-expiratory pressure elevations may cause overdistention of the lung and obscure a surfactant response. The general characteristics of a surfactant response need to be appreciated—a rapid improvement in oxygenation (an abrupt increase in FRC) followed by improved compliance in only some of the infants over the next minutes to hours. If FRC is greatly increased, positive end-expiratory pressures and/or rates need to be decreased. If compliance improves, peak pressures need to be decreased. However, decreasing pressures too rapidly in the absence of a compliance change obscures a surfactant response. The point is that the response depends on careful ventilatory management based on astute clinical observations of chest movement and an estimate of FRC. In my judgment, the pulmonary function tests now available for infants have not been demonstrated to be more sensitive than clinical observation for assessing ventilation requirements following surfactant treatments.

The Future

Surfactant has been evaluated systematically only for RDS and has been found to be effective in a large number of excellent trials. The type of surfactant, the dose, the frequency of doses, and the delivery systems will all probably be changed as more experience accumulates. Although instillation techniques work, perhaps aerosol techniques can be developed to optimize dose and distribution. Aerosolized surfactant was recently demonstrated to effectively treat RDS in preterm lambs.[56] Surfactant has been reported to be effective in some cases of pulmonary hypertension in newborns, and anecdotal reports exist of successful treatment of infants with meconium aspiration, at least one of which has been published.[57] Perhaps these treatments work because they overcome surfactant inactivation phenomena and/or because the infants treated had a secondary surfactant deficiency because of the lung injury resulting from treatment. Such uses of surfactant cannot be recommended until controlled clinical trials are completed. Trials are under way for the treatment of the adult respiratory distress syndrome (ARDS). This disease is much more complex in etiology than RDS, and surfactant treatments probably will be less effective although potentially useful. Surfactants also could be used as vehicles to distribute antibiotics or other drugs to the distal lung to treat a variety of lung diseases. The widespread use of surfactant will have a favorable impact on the respiratory care of preterm infants with RDS and perhaps on other groups of patients.

REFERENCES

1. Stern L. Hyaline membrane disease. Orlando FL: Grune and Stratton,1984.

2. Robertson B. Pathology and pathophysiology of neonatal surfactant deficiency. In: Robertson B, Van Golde LMG, Batenburg JJ, eds. Pulmonary surfactant. Amsterdam: Elsevier Science Publishers,1984:383-418.
3. Adams FH, Fujiwara T, Emmanouilides G. Lung phospholipid of the human fetus and infants with and without hyaline membrane disease. J Pediatr 1970;77:833-841.
4. Hallman M, Merritt TA, Pohjavuori M, Gluck L. Effect of surfactant substitution on lung effluent phospholipids in respiratory distress syndrome: Evaluation of surfactant phospholipid turnover, pool size, and the relationship to severity of respiratory failure. Pediatr Res 1986;20:1228-1235.
5. Jobe A, Ikegami M. Surfactant for the treatment of respiratory distress syndrome. Am Rev Respir Dis 1987; 136:1256-1275.
6. Jobe A, Ikegami M, Jacobs H, Jones S. Surfactant pool sizes and severity of RDS in prematurely delivered lambs. Am Rev Respir Dis 1983;127:751-755.
7. Ikegami M, Jobe A, Yamada T, Seidner S. Relationship between alveolar saturated phosphatidylcholine pool sizes and compliance of preterm rabbit lungs. Am Rev Respir Dis 1989;139:367-369.
8. Ikegami M, Jacobs H, Jobe A. Surfactant function in respiratory distress syndrome. J Pediatr 1983;102:443-447.
9. Ikegami M, Jobe AH, Glatz T. Surface activity following natural surfactant treatment in premature lambs. J Appl Physiol 1981;51:306-312.
10. Seeger W, Stohr G, Wolf HRD, Neuhof H. Alteration of surfactant function due to protein leakage: Special interaction with fibrin monomer. J Appl Physiol 1985; 58:326-338.
11. Jackson JC, MacKenzie AP, Chi EY, Standaert TA, Truog WE, Hodson WA. Mechanisms for reduced total lung capacity at birth and during hyaline membrane disease in premature newborn monkeys. Am Rev Respir Dis 1990;142:413-419.
12. Jobe A, Ikegami M, Jacobs H, Jones S, Conway D. Permeability of premature lamb lungs to protein and the effect of surfactant on that permeability. J Appl Physiol 1983;55:169-176.
13. Jobe A, Jacobs H, Ikegami M, Berry D. Lung protein leaks in ventilated lambs: Effect of gestational age. J Appl Physiol 1985;58:1246-1251.
14. Ikegami M, Jobe A, Pettenazzo A, Seidner SR, Berry DD, Ruffini L. Effects of maternal treatment with corticosteroids, T3, TRH and their combinations on lung function of ventilated preterm rabbits with and without surfactant treatments. Am Rev Respir Dis 1987; 136:892-898.
15. Jacobs H, Jobe A, Ikegami M, Jones S. Accumulation of alveolar surfactant following delivery and ventilation of premature lambs. Exp Lung Res 1985;8:125-140.
16. Jobe A. Metabolism of endogenous surfactant and exogenous surfactants for replacement therapy. Seminars Perinatol 1988;12:231-244.
17. Ikegami M, Jobe A, Yamada T, et al. Surfactant metabolism in surfactant-treated preterm ventilated lambs. J Appl Physiol 1989;67:429-437.
18. Jobe A, Ikegami M, Jacobs H, Jones S. Surfactant and pulmonary blood flow distributions following treatment of premature lambs with natural surfactant. J Clin Invest 1984;73:848-856.
19. Seidner S, Pettenazzo A, Ikegami M, Jobe A. Corticosteroid potentiation of surfactant dose response in preterm rabbits. J Appl Physiol 1988;64:2366-2371.
20. Ikegami M, Jobe A, Seidner S, Yamada T. Gestational effects of corticosteroids and surfactant in ventilated rabbits. Pediatr Res 1989;25:32-37.
21. Grossman G, Nilsson R, Robertson B. Scanning electron microscopy of epithelial lesions induced by artificial ventilation of the immature neonatal lung: The prophylactic effect of surfactant replacement. Eur J Pediatr 1986;145:361-367.
22. Merritt TA, Hallman M, Holcomb K, et al. Human surfactant treatment of severe respiratory distress syndrome: Pulmonary effluent indicators of lung inflammation. J Pediatr 1986;108:741-748.
23. Jobe AH, Ikegami M, Glatz T, Yoshida Y, Diakmanolis E, Padbury J. Duration and characteristics of treatment of premature lambs with natural surfactant. J Clin Invest 1981;67:370-375.
24. Vidyasagar D, Maeta H, Raju R, et al. Bovine surfactant (Surfactant-TA) therapy in immature baboons with hyaline membrane disease. Pediatrics 1985;75:1132-1142.
25. Davis J, Veness-Meehan K, Notter R, Bhutani V, Kendig J, Shapiro D. Changes in pulmonary mechanics after the administration of surfactant to infants with respiratory distress syndrome. N Engl J Med 1988; 319:476-479.
26. Couser R, Ferrara B, Ebert J, Hoekstra R, Fangman J. Effects of exogenous surfactant therapy on dynamic compliance during mechanical breathing in preterm infants with hyaline membrane disease. J Pediatr 1990;116:119-124.
27. Edburg KE, Ekstrom-Jodal B, Hallman M, Hjalmarson O, Sandberg K, Silberger A. Immediate effects on lung function of instilled human surfactant in mechanically ventilated newborn infants with IRDS. Acta Pediatr Scand 1990;79:750-755.
28. Noak G, Curstedt T, Grossman G, Nilsson R, Robertson B. Passive expiratory flow-volume recordings in immature newborn rabbits. Respiration 1990;57:1-5.
29. Gladstone I, Mecurio M, Devenny S, Jacobs H. Antenatal steroids, postnatal surfactant, and pulmonary function in premature rabbits. J Appl Physiol 1989;67:1377-1382
30. Fujiwara T, Chida S, Watabe Y, Maeta H, Morita T, Abe T. Artificial surfactant therapy in hyaline membrane disease. Lancet 1980;1:55-59.
31. Enhorning G. Artificial surfactant to prevent and treat neonatal respiratory distress syndrome. Pediatrics 1980;66:799-800.

32. Shapiro DL, Notter RH. Surfactant replacement therapy. New York: Alan R Liss Inc, 1989.
33. Exosurf Neonatal—Product Monograph. Research Triangle Park NC: Burroughs Wellcome Co, 1990.
34. Survanta Treatment Investigational New Drug Manual. Columbus OH: Ross Laboratories, 1989.
35. Hallman M, Merritt TA, Jarvenpaa A, et al. Exogenous human surfactant for treatment of severe respiratory distress syndrome: A randomized prospective clinical trial. J Pediatr 1985;106:963-969.
36. Merritt TA, Hallman M, Bloom BT, et al. Prophylactic treatment of very premature infants with human surfactant. N Engl J Med 1986;315:785-790.
37. Dunn M, Shennan AT, Possmayer F. Single- versus multiple-dose surfactant replacement therapy in neonates of 30 to 36 weeks' gestation with respiratory distress syndrome. Pediatrics 1990;86: 564-571.
38. Long W, Thompson T, Sundell H, Schumacher R, Volberg F, Guthrie R, and the American Neonatal Exosurf Study Group I. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700-1350 gram infants with respiratory distress syndrome. J Pediatr 1991; 118:595-606.
39. Enhorning G, Shennan A, Possmayer F, Dunn M, Chen CP, Milligan J. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant: A randomized clinical trial. Pediatrics 1985;76:145-153.
40. Kwong MS, Eagan EA, Notter RH, Shapiro DL. Double-blind clinical trial of calf lung surfactant extract for the prevention of hyaline membrane disease in extremely premature infants. Pediatrics 1985;76:585-592.
41. Kendig JW, Notter RH, Cox C, et al. Surfactant replacement therapy at birth: Final analysis of a clinical trial and comparisons with similar trials. Pediatrics 1988; 82:756-762.
42. Soll RF, Hoekstra RE, Fangman JJ, et al. Ross Collaborative Surfactant Prevention Study Group. Multicenter trial of single-dose modified bovine surfactant extract (Survanta) for prevention of respiratory distress syndrome. Pediatrics 1990;85:1092-1102.
43. Gitlin JD, Soll RF, Parad RB, et al. Randomized controlled trial of exogenous surfactant treatment of hyaline membrane disease. Pediatrics 1987;79:31-37.
44. Raju TN, Vidyasagar D, Bhat R, et al. Double-blind controlled trial of single-dose treatment with bovine surfactant in severe hyaline membrane disease. Lancet 1987;1:651-655.
45. Collaboratory European Multicenter Study Group. Surfactant replacement therapy for severe neonatal respiratory distress syndrome: An international randomized clinical trial. Pediatrics 1988;82:683-691.
46. Horbar JD, Soll RF, Sutherland JM, et al. A multicenter randomized placebo-controlled trial of surfactant therapy for respiratory distress syndrome. N Engl J Med 1989;320:959-965.
47. Lang MJ, Hall RT, Reddy NS, Kurth CG, Merritt TA. A controlled trial of human surfactant replacement therapy for severe respiratory distress syndrome in very low birthweight infants. J Pediatr 1990;116:295-300.
48. Morley CJ, Greenough A, Miller NG, et al. Randomized trial of artificial surfactant (ALEC) given at birth to babies from 23-34 weeks gestation. Early Human Devel 1988;17:41-54.
49. Konishi M, Fujiwara T, Naito T, et al. Surfactant replacement therapy in neonatal respiratory distress syndrome. Eur J Pediatr 1988;147:20-25.
50. Jobe AH. Lung maturational agents and surfactant treatments: Are they complementary in preterm infants? J Perinatol 1989;9:1418.
51 Thibeault DW, Beatty EC, Jr, Hall RT, Bowen SK, O'Neill DH. Neonatal pulmonary hypoplasia with premature rupture of fetal membranes and oligohydramnios. J Pediatr 1985;107:278-281.
52. Swischuk LE, Richardson CJ, Nichols MM, Ingman MJ. Primary pulmonary hypoplasia in the neonate. J Pediatr 1979;95:573-577.
53. Hislop, AA, Wigglesworth JS, Desai R. Alveolar development in the human fetus and infant. Early Hum Devel 1986;13:1-11.
54. Sherman MP, D'Ambola JB, Aeberhard EE, Barrett CT. Surfactant therapy of newborn rabbits impairs lung macrophage bactericidal activity. J Appl Physiol 1988; 65:137-145.
55. Fujiwara T, Konishi M, Chida S, Maeta H. Factors affecting the response to a postnatal single dose of a reconstituted bovine surfactant (Surfactant TA). In: Lachman B, ed. Surfactant replacement therapy. Berlin: Springer-Verlag, 1988:91-107.
56. Lewis J, Ikegami M, Jobe A, Tabor B. Aerosolized surfactant treatment in preterm lambs. J Appl Physiol 1991;70:869-876.
57. Auten RL, Notter RH, Kendig JW, Davis J, Shapiro DL. Surfactant treatment of full term newborns with respiratory failure. Pediatrics 1991;87:101-107.

Jobe Discussion

Martin: Would you expect primarily improvement in FRC, lung compliance, or both in response to surfactant therapy?

Jobe: In animal models of surfactant treatment, both FRC and compliance change. Clinically, we do not know how uniform inflation will be following surfactant administration. Empirically, following Survanta® treatment, the lungs of infants often move up the pressure-volume curve. Following surfactant instillation, the P_{O_2} increases immediately and F_{IO_2} is decreased. However, P_{CO_2} may be somewhat elevated relative to the

pretreatment value. Since P_{CO_2} has increased, the standard response would be to increase ventilation (rate or pressure); however, by clinical exam the chest seems more expanded. In several such cases, I have turned down peak and expiratory pressures with a resultant visual increase in tidal volume and a large fall in P_{CO_2}. The major effect of surfactant treatments is on lung volumes. Some of the volume increase represents opening gas exchange surface, but some may represent gas trapping behind airways temporarily obstructed with the surfactant suspension. I think it's important to separate the oxygenation response from the ventilatory response to surfactant in interpreting clinical responses.

Dr Fujiwara in Japan feels that better clinical responses will result from the use of relatively long inspiratory times and moderate rates resulting in relatively large tidal volume ventilation. Such a style should more rapidly deliver the surfactant to the distal lung and minimize airway obstruction.

Chatburn: I've heard anecdotal reports from several centers about pulmonary hemorrhage after surfactant administration. Have you seen this? And, could you comment on the possible causes?

Jobe: Pulmonary hemorrhage has been noted with surfactant treatments in this country, although the incidence has not been well-documented in the published clinical trials.[1] Pulmonary hemorrhage was not a prospectively defined endpoint, and thus incidences between studies cannot be compared. Pulmonary hemorrhage is a known complication of RDS, especially in very tiny infants, and the influence of surfactant treatments on the incidence of pulmonary hemorrhage may, in part, be a problem of perception. Since surfactant saves lives, perhaps some of these infants would have died with clinically inapparent pulmonary hemorrhage, a diagnosis often made at autopsy. On the other hand, nonuniform lung distention could cause tissue shear forces and result in hemorrhage. The Burroughs Wellcome people have associated pulmonary hemorrhage with patent ductus arteriosus in their trials,[2] although I find that a tenuous association. Pulmonary hemorrhage may be the only significant complication of surfactant treatments noted to date.

1. Bose C, Corbet A, Bose G, et al. Improved outcome at 28 days of age for very low birth weight infants treated with a single dose of synthetic surfactant. J Pediatr 1990;117:947-953.
2. Exosurf® product information. Research Triangle Park NC: Burroughs Wellcome Co.

Stark: Alan (Jobe), I wonder if you would comment on the relative merits of surfactant preparations, with and without protein?

Jobe: Presently, a synthetic surfactant, Exosurf, is the only licensed surfactant for clinical use. It contains no protein. Surfactants prepared from animal lungs or alveolar washes are licensed in Europe and Japan, and Survanta is one such surfactant extensively evaluated in this country. These surfactants contain the surfactant-specific proteins SP-B and SP-C, and the animal data and clinical impressions are that they have more immediate physiologic effects. However, both synthetic and animal-source surfactants decrease mortality and lung-related morbidity. No direct comparisons have been published.

Salyer: Could you comment on the need for volume monitoring of ventilation around the time of surfactant administration and also on the method of administration—rolling from side to side?

Jobe: Monitoring of lung volumes is just not practical because there is no reliable equipment available for such measurements. Plethysmography is not practical in sick infants on a routine basis, and washout techniques are hampered by the need for high F_{IO_2} and gas trapping. A compliance measurement alone is not very helpful if lung volume is not known. I think that a lot of information can result from looking at the patient's chest; perhaps there's still an art to neonatal respiratory care.

Surfactants are administered by instilling 3-5 mL/kg suspensions of surfactant into the trachea of an infant while positioning the infant in an attempt to optimize distribution. Exosurf and Survanta are given by slightly different protocols, but neither has been demonstrated to be superior. The treatment techniques are quite empiric.

There are at least 3 specific proteins in mammalian surfactant. Sp-A is a highly glycosylated protein having a monomer molecular weight of about 36 Kd and a multimer molecular weight of about 650 Kd. SP-B and SP-C are very hydrophobic proteins of less than 6 Kd that are thought to be the major proteins responsible for the biophysical properties of surfactant. All animal source surfactants contain SP-B and SP-C, while SP-A is in none of the surfactants presently being developed commercially. SP-A may not be included in the second-generation human-gene-product surfactants because it is such a complex molecule and it does not seem to have a critical function, at least for infants. SP-A is a multifunctional protein involved in regulation of surfactant secretion and uptake as well as perhaps macrophage function. However, surfactants with only SP-B and/or SP-C can have very good function when tested clinically.

Rau: I have a question about the nebulization of surfactant. Administration by aerosol seems to be more time-intensive and, related to that, more equipment-intensive, compared

to the instillation procedure. Is it superior or what is the rationale for pursuing that method of administration from what you've seen so far?

Jobe: While more equipment would be required for aerosol treatments, the treatment itself would be "kinder and gentler" because a large volume of saline would not be acutely dumped into the lungs, resulting in transient airway obstruction. Also, the distribution of surfactant might be more uniform throughout the lung. The real interest in aerosol therapy is for surfactant in ARDS. The adult pulmonologist is not at all enthusiastic about pouring 280 mL (4mL/kg × 70 kg) of saline into the lungs of a patient with respiratory failure.

Rau: A quick follow-up to that. How do you handle the problem of keeping submicronic particles in suspension? Do you find that they do not remain in suspension—because that seems to be a problem with decreased particle size?

Jobe: In our aerosol studies with surfactant, aerosol was generated during inspiration directly from the aerosolizer.[1] There were not losses by settling, although impaction on acute angles in the system was a problem.

1. Lewis JF, Ikegami M, Jobe AH, Tabor B. Aerosolized surfactant treatment of preterm lambs. J Appl Physiol 1991;70:869-876.

Rau: Right, with any aerosol as you decrease to submicronic size, the tendency to remain in suspension becomes greater and the aerosol is often exhaled in some studies.[1,2] Has that not been a problem?

1. Newman SP, Clarke SW. Therapeutic aerosols 1—Physical and practical considerations (editorial). Thorax 1983;38:881-886.
2. Morrow PE. Aerosol characterization and deposition. Am Rev Respir Dis 1974;110:88-99.

Jobe: Smaller particles will not be lost in the proximal airways and at least will reach the respiratory surface, although many will remain in suspension and be exhaled. There is no information on the ideal particle size for surfactant or even where in the lung deposition would be optimal for the best clinical response.

Long-Term Outcome of Respiratory Distress in Infants

Avroy A Fanaroff MB, Richard J Martin MB BS, and Maureen Hack MB ChB

Introduction

Improved technology and better understanding of the pathophysiology have markedly reduced the mortality in many neonatal respiratory disorders.[1] Relatively newer therapies including surfactant administration, steroid therapy, and extracorporeal membrane oxygenation appear to have improved the outcome for many preterm and term infants.[2-4] Preliminary follow-up data suggest that this improved survival has not been associated with increases in unfortunate pulmonary or neurodevelopmental sequelae. It is imperative that we follow these survivors closely to determine their later performance and to identify any long-term morbidity. In this paper, I present an overview of the outcome of neonatal respiratory disorders.

Background

Many problems are inherent in the establishing of a follow-up program, and outcome reports contain many flaws. Many reports are hospital- or center-based and may include inborn and/or outborn infants. Both populations incorporate an inherent selection bias. Inborn populations are influenced by the referral patterns and may include maternal transports to the center, whereas transported infants may have received less optimal initial care or may include only the sickest infants. Few studies evaluate total geographic regions, including all infants born therein because such studies are economically taxing, logistically difficult, and tend to use screening evaluations rather than in-depth assessments. Randomized clinical trials with appropriately matched controls are the exception rather than the rule. In all studies, it is essential to control for sociodemographic status, which has a dominant effect on outcome. Other factors to be considered when evaluating outcome are the number of infants lost to follow-up, postdischarge deaths, and the standardization of the age and method of follow-up. In addition, the important concept of the continuum of environmental risk that predisposes an individual to perinatal risk and also influences later growth and development should be addressed. Parmelee,[5] for example, has shown the buffering effect that an optimal family environment may have in ameliorating a biologic risk factor. Preterm infants with an abnormal electroencephalogram (EEG) at 40-weeks corrected age were noted to have a low intelligence quotient (IQ) unless they had been reared in a consistently responsive environment, in which case their IQ was similar to those neonates with no EEG abnormalities.

In my experience, the optimal follow-up program repeatedly assesses growth and neurodevelopmental status, documents the presence of chronic disease, intercurrent illness, and the need for rehospitalization, and evaluates the special

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Abbreviations Used in This Paper

BPD	— bronchopulmonary dysplasia
BW	— birthweight
CLD	— chronic lung disease
CO_2	— carbon dioxide
DQ	— developmental quotient
EEG	— electroencephalogram
FRC	— functional residual capacity
GA	— gestational age
IQ	— intelligence quotient
IVH	— intraventricular hemorrhage
LBW	— low birthweight
NICHD	— National Institute of Child Health and Development
RDS	— respiratory distress syndrome
SD	— standard deviation
VLBW	— very low birthweight

senses, including vision and hearing. Ongoing evaluations to observe behavior and school performance are desirable.

Respiratory Distress Syndrome and Outcome

The emergence of chronic lung disease as a common problem in infants presents a major challenge to neonatologists. Preterm infants with acute pulmonary disease, predominantly respiratory distress syndrome (RDS), make a rapid and apparently complete recovery and subsequently appear to have entirely normal lungs. The term bronchopulmonary dysplasia (BPD) was introduced in 1967 by Northway and colleagues[6] to describe a sequence of clinical and radiographic pulmonary changes that developed over weeks in a group of infants with RDS, following prolonged assisted ventilation and exposure to high inspired oxygen concentration. Subsequent reports[7,8] have described a similar chronic course after prolonged assisted ventilation in infants with meconium aspiration syndrome, persistent fetal circulation, diaphragmatic hernia, and neonatal pneumonia.

BPD is now recognized as a disease with a much broader spectrum of clinical severity than the severe cystic emphysema originally documented by Northway. Bancalari and Gerhardt[7] have defined BPD as existing in infants who require mechanical ventilation during the first week, are oxygen-dependent after at least 28 days, and exhibit persistent increased densities with or without hyperinflation on chest radiographs. The incidence of BPD in infants who develop RDS and require assisted ventilation but survive is estimated to be between 10 and 20%, but is greater in lower birthweight (BW) infants, exceeding 50% in those < 750 g and 40% for those between 750 and 1,000 g. Shennan and associates[9] in 1988 reported that, whereas the need for oxygen at 28 days is a good predictor of abnormal finding in infants beyond 30-weeks gestation at birth, it is not very useful in infants of lesser gestational age. However, irrespective of gestational age (GA) at birth, the need for additional oxygen at 36-weeks-corrected postgestational age is an excellent predictor of abnormal outcome (63%).[9] The positive predictability of this simple indicator (ie, 90% chance of normality if there is no oxygen requirement at this point in life) makes this an attractive marker for morbidity.

Changes in patterns of care,. with more aggressive management of low-birthweight (LBW) infants are reflected in Table 1 from Rainbow Babies and Childrens Hospital. Note the increased use of mechanical ventilation and increased incidence of oxygen dependency at 28 days. With the survival of smaller infants, the duration of oxygen need relates to BW as reflected in Figure 1 from the National Institute of Child Health and Development (NICHD) Neonatal Research Network. The survival of smaller, less mature infants has been accompanied by an increased number of infants with chronic lung disease (CLD).

Children who have had RDS, especially those who develop BPD, have a poorer outcome. Physical growth and ultimate body size, although strongly influenced by genetic potential, provide a highly sensitive index of the effects of early environmental events on the developing organism. Thus, any deviation from the normal trajectory of growth provides an easily documentable, yet important outcome measure. Close monitoring of weight length and head circumference yield important prognostic information.[11]

In follow-up of a cohort of very-low-birthweight (VLBW) infants delivered in 1977 and 1978, my group[11] documented that 58% of the infants suf-

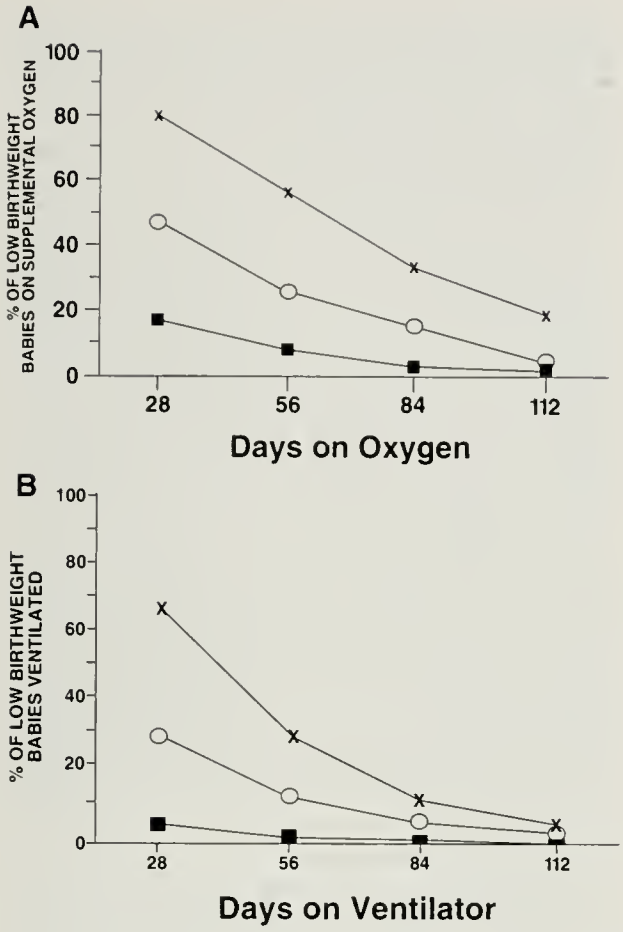

Fig. 1. X = 501-750 g; O = 751-1000 g; ■= 1001-1500 g. A. Relationship between birthweight and percent of infants on and duration of administration of supplemental oxygen. B. Relationship between birthweight and percent of infants on and duration of mechanical ventilation. (Reprinted, with permission, from Reference 10.)

fered from intrauterine and or neonatal growth failure. Infants who failed to thrive either in the nursery or after discharge were more likely to have persistence of pulmonary (bronchopulmonary dysplasia, or BPD) and gastrointestinal complications (cholestasis and necrotizing enterocolitis), and more likely to require rehospitalization. Furthermore, those infants whose growth failed to catch up by 8-months corrected age had a lower developmental quotient (DQ) and a higher incidence of neurologic abnormalities. Poor head growth, resulting from asymmetrical growth retardation in-utero, and/or poor neonatal head growth, may be one of the most important determinants of outcome.

The primary teeth may be used as markers of intrauterine and postnatal insults. Enamel hypoplasia, known since prehistoric times, has been documented in 40% of LBW infants. The degree of hypocalcification correlates with duration of oxygen therapy and with arterial and carbon dioxide tension on admission to the neonatal intensive care unit (hypocalcification occurring with elevated CO_2 and relatively low P_{aO_2}).[12,13] From the other perspective, poor growth and neurodevelopmental outcome have been well-documented among infants with CLD. However, the reports,[14-17] mainly before 1983, have been limited in usefulness by varied definitions of BPD, small sample sizes, heterogeneous subjects, and lack of controls. I believe that more recent survivors with CLD represent a different population of smaller, less mature infants at greater risk for intraventricular hemorrhage (IVH).

Neurodevelopmental Outcome Associated with Respiratory Disorders

The incidence of neurologic and developmental deficits in survivors with BPD varies widely, related in large part to differences in patient selection criteria. Shankaran et al[18] related developmental indices to the length of time that the infants received supplemental oxygen. In a small series, she and her co-workers noted that infants with subnormal developmental scores had a mean time in oxygen of 84 days versus a mean of 46 days in oxygen for those with normal scores.[18] Thus, outcome could be related to severity of pulmonary disease as reflected in the need for prolonged oxygen therapy. Several studies[14-17] have demonstrated a higher incidence of growth and developmental delays in infants with BPD, using the Northway criteria for diagnosis of BPD. There is less evidence for developmental impairment in BPD infants when diagnostic criteria for CLD have been liberalized and are based primarily on oxygen requirement at 28 days.

Skidmore et al[14] wished to determine the incidence of cerebral palsy and other forms of neurodevelopmental impairment in VLBW infants (< 1500 g) born during 1983 and 1984 who developed CLD. These children were compared with LBW in-

fants, born during the same period, but with less severe or no lung disease. Of 343 infants admitted, 272 survived to 28 days of life, 17 infants died between 28 days and 2 years of life. She and her coworkers were able to prospectively follow 249 (98%) of the 255 surviving infants to at least 20-months corrected age. The infants on admission had a mean (SD) BW of 1,148 (225) g, and a mean (SD) GA of 29 (3) weeks; 63% were black, 43% were boys, and 76% were in the lower socioeconomic classes. Of the survivors, 84 required oxygen for 2 days or less, 113 for 3-27 days, and 52 for ≥ 28 days (Table 2). The incidence of CLD was 21%, overall, but 71% for infants < 750 grams, 43% for those between 750 and 999 grams, and 11% between 1,000 and 1,499 grams. The maternal demographic data, including education and social class, were similar in all three groups. The 52 surviving infants with CLD were significantly younger and smaller than infants who required less oxygen (mean BW 959g GA 27 wk). Infants with CLD had significantly lower 1- and 5-minute Apgar scores and had higher rates of apnea, sepsis, and patent ductus arteriosus. Additionally, 43% of infants with CLD had Grades 3 and 4 IVH, compared with 14% in each of the other 2 groups. This higher rate of neonatal sequelae for infants with CLD was probably related to their lower BW, younger GA, and greater severity of lung disease, and was associated with significantly longer hospital stays.

Table 2. Neurologic and Developmental Outcome at 20 Months*

Outcome	Duration of Oxygen Dependence			
	< 2 days (n = 84) %	3-27 days (n = 113) %	> 28 days (n = 52) %	Total (n = 249) %
Neurologic impairment	6†	9†	29†	12
Hydrocephalus (shunted)	-	1	2	1
Cerebral palsy	4‡	4‡	15‡	6
Hypo/hypertonia	1	3	6	3
Severe visual impairment	1	1	2	1
Severe hearing impairment	1	1	2	1
Congenital malformations	1	2	6	2
Isolated low DQ (< 80)	8	11	8	9
TOTAL Impaired	16†	21†	42†‡	24

*Data based on Reference 14.
†$p < 0.001$.
‡$p < 0.01$.

Whereas the overall incidence of cerebral palsy was 5.6%, 8/52 (15%) with CLD had cerebral palsy (Table 2). Four of these infants also had hydrocephalus requiring a shunt. In contrast, 2.7% of infants requiring oxygen for between 3 and 27 days developed cerebral palsy and 3.6% of those requiring oxygen for 2 days or less were found with cerebral palsy ($p < 0.01$).

The overall neurodevelopmental impairment rate was 24%, including 12% with neurologic deficits, 2% with major malformations, and 9% with a subnormal DQ (< 80) but normal neurologic examination. Infants with CLD had a neurologic impairment rate of 29%. This was significantly higher than for the group requiring supplemental oxygen for < 2 days (6%), and 3-27 days (9%) ($p < 0.001$) and could be attributed to the high rates of cerebral palsy and/or shunt-dependent hydrocephalus.

Children with CLD also had significantly lower Bayley motor, mental, and mean scores, compared to subjects in the other two groups. Their mean (SD) motor score was 81 (20) compared to 94 (24) infants in oxygen for < 2 days; and 93 (21) for those in oxygen for 3-27 days ($p < 0.001$). The mean mental score was 84 (22) compared to 23(18) and 94 (16) for the other two groups ($p < 0.05$).

In summary, VLBW infants with CLD who require oxygen for ≥ 28 days have a poorer outcome, including a higher rate of cerebral palsy (15%) and other neurodevelopmental disorders, compared to infants with less severe lung disease. Most infants with mild-to-moderate lung disease requiring oxygen for < 28 days are indistinguishable from their healthy counterparts by 2 years of age. The infant with CLD is at highest risk in the VLBW population. In addition to the problems associated with extreme immaturity, complicated birth, low Apgar scores, IVH, and neonatal infection, these babies bear the additional burden of prolonged ventilator and oxygen dependence and repeated episodes of hypoxia and acidosis. The combination of these

complications (particularly hypoxic, ischemic cerebral injury and IVH) may compound the risk and account for the high incidence of cerebral palsy. Thus, 22 of the infants with CLD also had Grades 3 or 4 IVH, among whom 8 (36%) developed cerebral palsy. Thus, the combination of severe IVH and CLD was a strong risk factor for the development of cerebral palsy.

The association between CLD, cerebral palsy, and other forms of neurologic impairment has been well-recognized (Table 3). Among 21 VLBW infants with BPD, Vohr and colleagues[15] reported 24% with cerebral palsy and 35% with neurologic impairments. In 16 BPD infants followed by Yu et al,[16] 18% were found to have cerebral palsy and 29% neurologic impairment. Sauve and Saigal[19] describe cerebral palsy in 11% and neurologic impairment in 17% of a cohort of 141 infants with BPD, 85% of whom had birthweights < 1500 g. Koops et al[17], in 1984, reported 13% cerebral palsy and 27% neurologic impairment in 30 infants with BW ranging from 540 to 2380 g. Saigal and O'Brodovich[20] have analyzed long-term outcome in a 1987 review.

Table 3. Incidence of Cerebral Palsy and Neurologic Impairment in Low Birthweight Infants with Bronchopulmonary Dysplasia

			BPD Outcome	
Author	Year	n	Cerebral Palsy	Neuro-impaired
Vohr et al[15]	1982	21	24%	35%
Yu et al[16]	1983	16	18%	29%
Sauve et al[19]	1985	141	11%	17%
Koops et al[17]	1984	30*	13%	27%
Skidmore et al[14]	1990	52†	15%	29%

* 85% < 1.5 kg.
†0.54-2.38 kg.

The long-term outcome for infants with CLD clearly depends on the extent of their initial disease. A small but significant proportion of infants with severe BPD die prior to or shortly after discharge from the hospital. Although often labeled as episodes of sudden infant death, this outcome may be associated with acute respiratory infections or cardiac failure triggered by myocardial ischemia or hypoxia-induced pulmonary hypertension. The prolonged hospital stay of severely affected infants can be reduced considerably if oxygen can be administered at home, and this should be encouraged if the home and parental environment are suitable. Benefits include improved parent-infant bonding and sensory stimulation, significant monetary savings, and decreased risk of nosocomially acquired respiratory pathogens.

Although the oldest survivors of BPD are barely 20 years old, increasing numbers of studies are being reported regarding the neurodevelopmental and pulmonary outcomes of these infants.

Pulmonary Function and Morbidity

Goldman et al[21] performed pulmonary function studies on high-risk infants during the first week of life to predict development of CLD. All enrolled infants required mechanical ventilation for RDS for at least 3 days. No differences in lung compliance and distribution of ventilation were seen between the infants who did and did not develop BPD. However, mean pulmonary resistance in the infants who developed BPD was approximately 90% higher than that of those who did not. Unfortunately, these data only allow us to speculate whether high resistance is contributing to lung damage or is an early manifestation of CLD itself. High resistance could result from mechanical airway damage or peribronchial edema secondary to heart failure. I believe that we must have considerably more evidence and a clearer understanding of underlying mechanisms before early elevation of pulmonary resistance can be used as a marker for BPD.

Bronchodilators play an important role in acute management of BPD indicating that the airway obstruction is at least partially reversible. However, the impact of such therapy on long-term outcome is unknown. In addition, theophylline has other potential effects than bronchodilation, such as a decrease in respiratory pauses and enhanced diaphragmatic contractility.[22]

Healthy preterm infants have been thought to have insufficient bronchial smooth muscle to produce bronchoconstriction of any consequence, al-

though objective data are lacking. Nonetheless, infants with BPD do have pathologic evidence of bronchiolar smooth-muscle hypertrophy. Motoyama et al[23] evaluated deflation flow-volume curves, a possibly sensitive index of lower airway function, in sedated, ventilated preterm infants developing BPD. Airway reactivity was defined by an increase in respiratory flow at a fixed volume in response to a bronchodilator aerosol. Infants with developing chronic lung injury demonstrated relief of lower airway obstruction by 2-4 weeks postnatal age. Severity of airway reactivity at initial testing during the first postnatal weeks seemed to predict the severity and duration of respiratory failure. Thus, increased airway reactivity may lead to bronchospasm early in postnatal life. Its role in the longer-term outcome of BPD needs further study.

Sauve and Singhal[19] compared the outcome of a large number of infants diagnosed as having BPD between 1975 and 1982 to outcome of infants in a control group who also received assisted ventilation during the first week of life. Lower respiratory tract infections and rehospitalization for respiratory illnesses were significantly more common in the BPD group, but only during the first year of life. The incidence of multiple upper respiratory infections appeared comparable between groups at all ages. These data are encouraging for longer-term morbidity and in keeping with the tendency for BPD to improve over time. Myers et al[24] prospectively compared the frequency and severity of subsequent respiratory illness over the first 12 months between preterm infants with or without a history of RDS and term infants. Overall, preterm infants did not demonstrate an inherent risk for subsequent respiratory infection when compared to term infants. However, infants who survived RDS and developed residual lung disease had both more frequent and more severe respiratory illnesses over the first year. The data, thus, also suggest that later respiratory morbidity is a consequence of residual pulmonary abnormalities apparent on chest radiograph at discharge from the nursery and consistent with most diagnostic criteria for BPD.

Concurrent with these evaluations of persistent respiratory symptoms in infants, lung function has been systematically determined in infants with CLD. Tepper et al[25] evaluated lung function during the first year of life in infants with BPD (as diagnosed by Northway's criteria) and age-matched controls. In addition to a low functional residual capacity (FRC), BPD infants at 1 year of age had flattened expiratory flow-volume curves and very limited expiratory flow reserve during rapid chest compression (Fig. 2). These data suggest abnormal functional development in the infants' small airways. Unlike the alveoli, the absolute number of conducting airways is fixed prior to the neonatal period. It is unclear whether the documented changes in resistance are the result of neonatal lung injury or whether the early injury has interfered with subsequent normal growth and development.

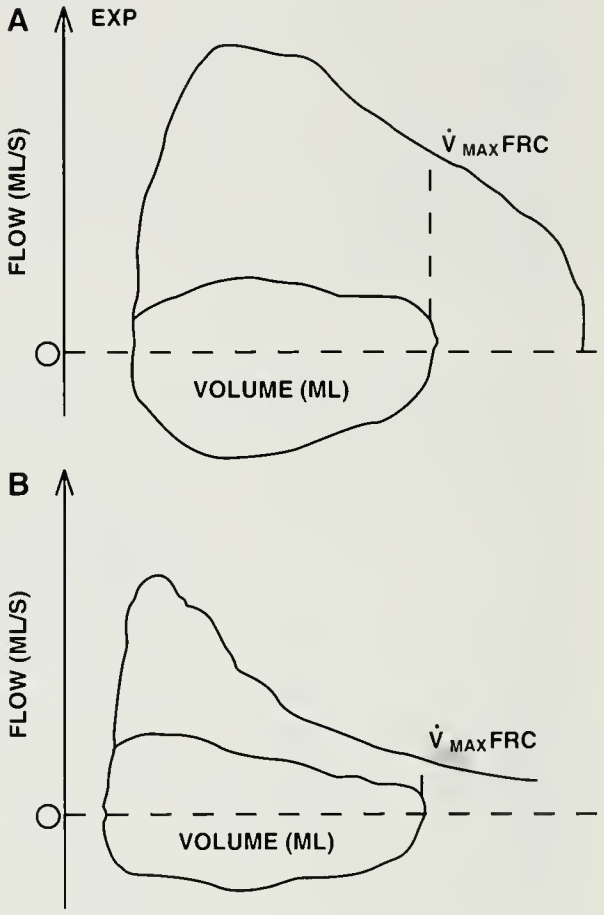

Fig. 2. A. Flow-volume curve typical of normal control infant. B. Flattened flow-volume curve and reduced FRC typical of infants with bronchopulmonary dysplasia.

Gerhardt et al[26] measured pulmonary function over the first 36 months in 39 infants with BPD and 40 normal growing infants who served as controls.

Many of the infants with BPD did have milder disease defined as 28 days of supplemental oxygen and persistent but nonspecific radiographic changes. FRC corrected for BW was decreased over the first 6 months, but then normalized with no evidence of gas trapping (Fig. 3). Lung compliance values were initially subnormal but increased to near normal levels by 3 years. The close correlation between compliance and weight suggests that the observed increase in compliance with age is related to lung growth and formation of new alveoli. Finally, pulmonary conductance values were initially low, increased little during the first 6 months, but then reached 85% of normal levels by 3 years of age. Thus, increased pulmonary resistance did not appear to be a major residual problem in those infants whose pulmonary function was steadily improving with growth.

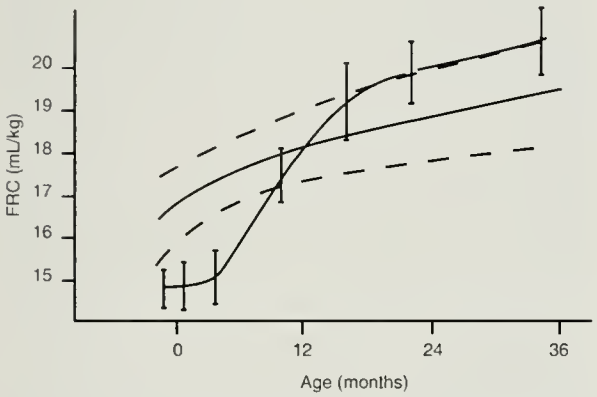

Fig. 3. Sequential measurements of functional residual capacity (FRC) expressed as FRC/kg bodyweight (with standard error of the mean, or SEM indicated, by vertical bars) in infants with chronic lung disease. For comparison, the curve for normal infants with 95% confidence limits is also shown. The data indicate that FRC corrected for weight, increases to the normal range by approximately 18 months in this group of infants. (Reprinted, with permission, from Reference 26.)

Several years earlier, Smyth and co-workers[27] studied 9 infants with BPD at a mean age of 8 years. In this group, persistent respiratory symptoms were common with both air trapping and abnormal chest radiographs. Spirometry demonstrated evidence of airway obstruction, and salbutamol aerosol inhalation improved forced expiratory flow in many of the group. Thus, at least for some children, abnormal pulmonary function does not resolve in early childhood. Persistence of airway damage is the likely cause of their airway hyperactivity and frequent wheezing episodes. Although a high incidence of asthma has been reported in the families of infants with BPD, suggesting a genetic predisposition to airway hyperactivity in BPD, this remains controversial. Bertrand et al[28] have studied 7-to-12-year-old survivors of RDS, comparable preterm infants without history of lung disease, and their siblings. Airway reactivity was positive in both preterm groups compared to term infants. The authors concluded that (1) infants with RDS have evidence of airway reactivity as a consequence of RDS severity and its treatment and (2) preterm infants without RDS have airflow limitation related to familial airway hyperreactivity. This led the investigators to speculate that unexplained premature labor may share a common pathway with airway lability. In severely affected children, pulmonary vascular resistance may remain elevated, and fall in response to oxygen administration, resembling the findings in adults with COPD.

Gerhardt et al[26] measured lung function before discharge in 53 infants who had been mechanically ventilated from the first day of life—26 by conventional ventilation and 27 by high-frequency ventilation. The groups were similar in terms of BW, GA, age, and duration of ventilatory and oxygen support. The infants were tested at age 10 weeks (Table 4). Both groups still had abnormal lung function with decreased compliance and increased resistance. However, FRC was in the normal range. No significant differences were found within the groups, refuting the hypothesis that high-frequency

Table 4. Comparison of Pulmonary Function at Follow-Up in Low-Birthweight Babies Ventilated by Conventional Ventilator (CV) and Oscillator (HFOV)

Subject Variable	CV (n = 26)	HFOV (n = 27)
Weight (g)	1830 ± 340	1830 ± 290
Age (d)	68 ± 24	70 ± 31
Lung compliance (mL/cm H_2O)	1.65 ± 24	1.54 ± 0.36
Airways resistance (cm $H_2O \cdot s \cdot L^{-1}$)	102 ± 24	107 ± 36
Functional residual capacity (mL)	30.6 ± 6	28.2 ± 10.7

oscillatory ventilation reduces the risk of lung damage to preterm infants.

Lebourges and colleagues[29] re-evaluated pulmonary function in childhood (ages 5-7 y) in 19 prematurely born infants (including 3 with BPD) who had required mechanical ventilation from 3 to 18 days. The follow-up evaluation revealed elevated resistance and reduced dynamic compliance. From infancy to childhood, elevated resistance persisted with mean (SD) values of 9.33 (2.51) vs 6.5 (1.52) cm $H_2O \cdot L \cdot s^{-1}$, $p < 0.01$), and dynamic compliance was significantly reduced compared to term infants. Maximum flow at FRC was significantly reduced, but diffusing capacity for carbon monoxide was similar to controls. Thus, persistent abnormalities in pulmonary function were documented, including increased airway obstruction but not hyperinflation. Ongoing evaluations are needed to document the natural history of this disorder.

Northway et al[30] studied 22 survivors of Stage IV BPD, who had been treated in the neonatal intensive care unit between 1965 and 1973, at age 17 years (range 13.9-23.1 y) for late outcome. The infants had been born at a mean (SD) GA of 33 (1) wk and a mean (SD) BW of 1,810 (150) g. Control groups consisted of 20 age-matched subjects, born prematurely without lung disease, and 48 normal-aged matched nonsmoking subjects. The assessment was performed by questionnaire interview, physician examination, chest x-ray, electrocardiogram, echocardiogram with Doppler, pulse oximetry, capillary blood gas, serum IgE, radioallergosorbent test (RAST), and pulmonary function tests. The ex-BPD subjects were significantly shorter than the ex-premature or normal subjects. Furthermore, the young adults with prior BPD have sequelae of airflow obstruction, hyperinflation, reactive airway disease, and, perhaps, even parenchymal disease up to 23 years after the clinical onset of disease (Table 5).

Table 5. Comparison of Pulmonary Function and Incidence of Reactive Airways Disease (RAD) in Subjects with Bronchopulmonary Dysplasia, Prematurity without BPD, and Controls: A 23-Year Follow-up*

Group	FEV_1 (% Pred)	RV/TLC (%)	RAD
BPD	76.8 ± 3.5†	122.6 ± 6.8†	11/29†
Preterm	96.3 ± 2.4	91.9 ± 6.5	10/20
Control	100.4 ± 1.7	97.7 ± 32.6	14/48

*From Reference 30
†$p < 0.05$.

Surfactant Treatment and Outcome

The short-term effects of surfactant therapy include improved survival, evidence of less severe respiratory distress, a decrease in air leaks including pulmonary interstitial emphysema and pneumothorax, and, in some reports, a suggestion of a lower incidence of CLD. To date, follow-up studies of randomized controlled trials of surfactant therapy include 599 surviving children (308 experimental, 291 controls). Of 525, 88% have been followed, with ages ranging from 12-60 months but with the majority followed for only 24 months (Table 6). Each study has been small, with the exception of Morley,[2] and follow-up rates range from 29-80%. No differences have been noted in post-discharge morbidity, including the rates of re-hospitalization, respiratory infection, allergy (including wheezing, skin rashes, and feeding intolerance) and growth and neurodevelopmental outcome. Dunn et al, [35] in a small study, noted an increase in major neurodevelopmental handicap among the surfactant-treated group, 5 subjects versus 2 subjects in the controls, whereas Vaucher et al[36] reported in a 1990 abstract that more of the controls had developmental delay (41% versus

Table 6. Outcome with Surfactant Therapy: A Composite Profile from Eight Studies*

Outcome	Surfactant n = 308	Control n = 291
Cerebral palsy	13%	11%
Rehospitalization	39%	44%
Respiratory infections	34%	40%
Wheezing	13%	17%
Skin allergy	12%	13%
Food allergy	11%	10%

* Follow-up rate = 88%.
From References 2, 15, 31-36.

23% of the experimental group). Vaucher et al have suggested that the outcome of children receiving rescue therapy is superior to prophylactic (delivery room) therapy with surfactant. Six of 35 infants who received rescue treatment with natural surfactant had severe mental and motor delay at 12 months compared to 18 of 33 who received prophylactic therapy. These are preliminary findings and longer follow-up is, of course, necessary to determine the overall effects of surfactant therapy.

Steroid Therapy and Outcome

Steroids have recently been utilized to wean infants from assisted ventilation and ameliorate BPD. Only Cummings et al[3] report on follow-up outcome. Thirty-six preterm infants (BW ≤ 1.25 kg, GA ≤ 30 wk) were randomized to receive dexamethasone for 42 days (n = 13), 18 days (n = 12), or not at all. At 6 months of age, 3 infants in the 18-day treatment and 2 in the control group were still on oxygen, and, at 15 months, 4 remained oxygen dependent. Follow-up to 15 months of age suggested a neurodevelopmental advantage for the infants treated with dexamethasone for 42 days as compared to the other two groups ($p < 0.05$). However, the few subjects and trivial differences in DQ make this a preliminary observation. Growth did not differ significantly among groups.

Effects of Assisted Ventilation on Outcome

The only major randomized controlled study of ventilator therapy on outcome is the recent study of the effects of high-frequency oscillatory ventilation (HFO) compared with conventional mechanical ventilation (CMV) in the treatment of respiratory failure. As part of a multicenter randomized clinical trial, 327 infants of BW 750-2,000 g were treated with HFO and compared to 346 infants who received CMV.[37,38] Survival and pulmonary morbidity was the same in both groups. At 16-24 months post-term age, 77% of survivors were examined (185 HFO and 201 CMV).[39] No difference was seen in growth, rate of rehospitalization (48% versus 46%), respiratory status, and cerebral palsy (11% versus 10%); however, a higher incidence of hydrocephalus was present in the HFV group (12% versus 6%, $p < 0.05$). The proportion of children with a normal neurodevelopmental status (Bayley > 83 and no major neurologic defect) tended to be less in the HFV group than in the CMV group (57% versus 66%, not a statistically significant difference). A higher rate of Grades 3 and 4 IVH in the HFV group (23% versus 11%) accounted for this difference (Table 7).

Table 7. Outcomes Observed in Follow-up of Assisted Ventilation by Conventional Ventilator (CV) and High Frequency Oscillator (HFO)*

Outcome	CV (n = 185)	HFO (n = 201)	p
Grade 3 & 4 IVH	11%	23%	< 0.05
Rehospitalization	46%	48%	NS
Cerebral palsy	10%	11%	NS
Hydrocephalus	6%	12%	< 0.05
Normal neurodevelopment	65%	54%	NS

* Data from References 37-39

Pulmonary Hypertension—ECMO and Hyperventilation

In addition to primary pulmonary hypertension, many respiratory disorders (including respiratory distress syndrome, pneumonia, meconium aspiration syndrome, and congenital diaphragmatic hernia) have been associated with pulmonary hypertension. In the past 5 years, infants not responding to conventional management with various approaches (including mechanical ventilation, paralysis, pressor agents, and pharmacologic manipulation of pulmonary flow) have been subjected to extracorporeal membrane oxygenation (ECMO). The ECMO registry now includes data from 72 centers and over 4,000 infants who have been treated. The survival rate for infants with a predicted mortality of > 80% (criteria for ECMO) has been 84%. Unfortunately, there is a paucity of information about both short- and long-term outcome following ECMO. Glass et al[4] noted that 65% of a group of 45 infants treated with ECMO were normal at 1 year and Schumacher et al[40] have reported that 80% of 92 infants followed were normal at

ages ranging between 1 and 7 years. Lott et al[41] confirmed continued reduced flow in the right internal carotid artery and a consistent reduction in the amplitude of right hemispheric long-latency evoked potentials. Few global hemispheric problems have been observed.

The outlook for conventionally managed infants with pulmonary hypertension is dismal. Bifano and Pfannenstiel[42] noted that only 49% of 21 infants were normal at 12 months among the 72% surviving pulmonary hypertension treated with hyperventilation. They observed that those infants with the poorest outcome had been hyperventilated the longest (mean [SD] =124 [52] h for abnormal versus 60 [53] h for normal, $p < 0.01$). Sell et al[43] reported a 60% incidence of neurodevelopmental abnormality accompanied by an unexplained 20% incidence of sensorineural hearing loss among survivors of persistent fetal circulation. Hendricks-Munoz et al[44] documented a 52.5% sensorineural hearing loss among 40 such infants. Hearing loss was again correlated with duration of ventilation and alkalosis.

These are disturbing outcome data. Many confounding variables may be present, not the least of which is the fact that these infants may have been severely hypoxic for periods of time. Nonetheless, despite the fact that it has never been subjected to rigorous study, hyperventilation is widely used. Hypocapnia results in cerebral vasoconstriction, reducing cerebral blood flow by almost one third. EEG abnormalities are produced in adults with hypocapnia, and increased brain lactate is noted in animals. In light of the developmental outcome noted, albeit from uncontrolled studies, it appears prudent to re-evaluate this practice. Furthermore, it is imperative that ECMO centers a priori identify control subjects who can be followed in parallel with the subjects undergoing bypass.

In Conclusion

The oldest survivors of chronic neonatal lung injury are only 20 years old. Therefore, long-term outlook well into adult life must remain speculative. As we await the results of long-term prospective studies of large numbers of BPD survivors, other factors such as infection, atopic disposition, smoking, air pollution, and socioeconomic factors inevitably complicate the issue. The impact of surfactant, steroids, high-frequency ventilation, and ECMO is becoming apparent. The prevention of further respiratory insult during childhood becomes mandatory in these patients. The use of both standard and new pediatric immunizations should be important to minimize further airway injury. RSV infection may prove lethal for oxygen-dependent, hospitalized infants with BPD. Both parental smoking and smoking by the patients themselves, as they grow into adolescence, should be vigorously discouraged. Overall, the short- and medium-term outlook for pulmonary function in the majority of survivors of prematurity with chronic neonatal lung disease remains very encouraging.

REFERENCES

1. Hack M, Fanaroff AA. Changes in the delivery room care of the extremely small infant (less than 750 g): Effects on morbidity and outcome. N Engl J Med 1986;314:660-664.
2. Morley CJ, Morley R. Follow up of premature babies treated with artificial surfactant (ALEC). Arch Dis Child 1990;65(7 spec no):667-669.
3. Cummings JJ, D'Eugenio DB, Gross SJ. A controlled trial of dexamethasone in preterm infants at high risk for bronchopulmonary dysplasia. N Engl J Med 1989;320:1505-1510.
4. Glass P, Miller M, Short B. Morbidity for survivors of extracorporeal membrane oxygenation: Neurodevelopmental outcome at 1 year of age. Pediatrics 1989;83:72-78.
5. Parmelee AH Jr. Sensory stimulation in the nursery: How much and when? J Dev Behav Pediatr 1985;6:242-243.
6. Northway WH Jr., Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. N Engl J Med 1976;276:357-368.
7. Bancalari E, Gerhardt T. Bronchopulmonary dysplasia. Pediatr Clin North Am 1986;33:1-23.
8. Tepper RS. Chronic respiratory disturbances in bronchopulmonary dysplasia. In: Bronchopulmonary dysplasia and related chronic respiratory disorders. Report of the 90th Ross Conference on Pediatric Research. Columbus OH: Ross Laboratories, March 1986:46-53.
9. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: Prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-532.
10. National Institute of Child Health and Development (NICHD) Neonatal Research Network.
11. Hack M, Breslau N, Fanaroff AA. Differential effects of intrauterine and postnatal brain growth failure in infants of very low birth weight. AJDC 1989;143:63-68.

12. Johnsen DC, Krejci C, Hack M, Fanaroff A. Localization of enamel hypoplasia and the association with respiratory distress in very low birthweight infants. J Dental Res 1984;63:59-64.
13. Seow WK, Humphreys C, Tudehope DI. Increased prevalence of developmental dental defects in low birthweight, prematurely born children: A controlled study. Pediatr Dent 1987;9:221-225.
14. Skidmore MD, Rivers A, Hack M. Increased risk of cerebral palsy among very low-birthweight infants with chronic lung disease. Dev Med Child Neurol 1990; 32:325-332.
15. Vohr BR, Bell EF, Oh W. Infants with bronchopulmonary dysplasia: Growth pattern and neurologic and developmental outcome. AJDC 1982;136:443-447.
16. Yu VY, Orgill AA, Lim SB, Bajuk B, Astbury J. Growth and development of very low birthweight infants recovering from bronchopulmonary dysplasia. Arch Dis Child 1983;58:791-794.
17. Koops BL, Abman Sh, Accurso FJ. Outpatient management and follow-up of bronchopulmonary dysplasia. Clin Perinatol 1984;11:101-122.
18. Shankaran S, Szego E, Eizert D, Siegel P. Severe bronchopulmonary dysplasia: Predictors of survival and outcome. Chest 1984;86:607-610.
19. Sauve RS, Singhal N. Long-term morbidity of infants with bronchopulmonary dysplasia. Pediatrics 1985;76:725-733.
20. Saigal S, O'Brodovich H. Long-term outcome of preterm infants with respiratory disease. Clin Perinatol 1987;14:635-650.
21. Goldman SL, Gerhardt T, Sonni R, et al. Early prediction of chronic lung disease by pulmonary function testing. J Pediatr 1983;102:613-617.
22. MF, Bairam A, Vert P. Neonatal apnea and apneic syndromes. Clin Perinatol 1987;14:3.
23. Motoyama EK, Fort MD, Klesh KW, Mutich RL, Guthrie RD. Early onset of airway reactivity in premature infants with bronchopulmonary dysplasia. Am Rev Respir Dis 1987;136:50-57.
24. Myers MG, McGuinness GA, Lachenbruch PA, Koontz FP, Hollingshead R, Olson DB. Respiratory illnesses in survivors of infant respiratory distress syndrome. Am Rev Respir Dis 1986;133:1011-1018.
25. Tepper RS, Morgan WJ, Cota K, Taussig LM. Expiratory flow limitation in infants with bronchopulmonary dysplasia. J Pediatr 1986;109:1040-1046.
26. Gerhardt T, Reifenberg L, Goldberg RN, Bancalari E. Pulmonary function in preterm infants whose lungs were ventilated conventionally or by high-frequency oscillation. J Pediatr 1989;115:121-126.
27. Smyth JA, Tabachnik E, Duncan WJ, Reilly BJ, Levison H. Pulmonary function and bronchial hyperactivity in long-term survivors of bronchopulmonary dysplasia. Pediatrics 1981;68:336-340.
28. Bertrand JM, Riley SP, Popkin J, Coates AL. The long-term pulmonary sequelae of prematurity: The role of familial airway hyperreactivity and the respiratory distress syndrome. N Engl J Med 1985;312:742-745.
29. Lebourges F, Moriette G, Boute M, Delaperche MF, Relier JP, Gaultier C. Pulmonary function in infancy and in childhood following mechanical ventilation in the neonatal period. Pediatr Pulmonol 1990;9:34-40.
30. Northway WH Jr, Moss RB, Carlisle KB, et al. Late pulmonary sequelae of bronchopulmonary dysplasia. N Engl J Med 1990;323:1793-1799.
31. Wilkinson A, Jenkins PA, Jeffrey J. Two controlled trials of dry artificial surfactant: Early effects and later outcome in babies with surfactant deficiency. Lancet 1985;2:287-291.
32. Halliday HL, McClure G, Reid MM. Growth and development two years after artificial surfactant replacement at birth. Early Human Develop 1986;13:323-327.
33. Msall ME, Rogers BT, Catanzaro N, Kwong, MA, Buck G. Five year neurodevelopmental outcome of infants less than 28 weeks gestational age enrolled in a surfactant randomized clinical trial (abstract). Pediatr Res 1989;20:258A.
34. Ware J, Taeusch HW, Soll RF, McCormick MC. Health and developmental outcomes of a surfactant controlled trial: Follow-up at 2 years. Pediatrics 1990;85:1103-1107.
35. Dunn MS, Sheenan AT, Hoskins EM, Lennox K, Enhorning G. Two-year follow-up of infants enrolled in a randomized trial of surfactant replacement therapy for prevention of neonatal respiratory distress syndrome. Pediatrics 1988;82:543-547.
36. Vaucher YE, Merritt TA, Hallman M, Harker LC, Wozniak PR, Gist K. Improved outcome following rescue versus prophylactive surfactant treatment in RDS (abstract). Pediatr Res 1990;27:260A.
37. Rigatto H, Davi M, Frantz ID III, et al. The HIFI Study Group. High- frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 1989;320:88-93.
38. The HIFI Study Group. High frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatemnt of respiratory failure in pretem infants: Neurodevelopmental status at 16 to 24 months of postterm age. J Pediatr 1990;117:939-945.
39. Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birthweight outcomes of the NICHD Neonatal Network. In press, 1990.
40. Schumacher RE, Palmer TW, Roloff DW, LaClair PA, Bartlett RH. Follow-up of infants treated with extracorporeal membrane oxygenation for newborn respiratory failure. Pediatrics 1991; 87:4.
41. Lott IT, McPherson D, Towne B, Johnson D, Starr A. Long-term neurophysiologic outcome after neonatal extracorporeal membrane oxygenation. J Pediatr 1990; 116:343-349

42. Bifano EM, Pfannenstiel A. Duration of hyperventilation and outcome in infants with persistent pulmonary hypertension. Pediatrics 1988;81:657-661.

43. Sell EL, Gaines JA, Gluckman C, Williams E. Persistent fetal circulation: Neurodevelopmental outcome. Am J Dis Child 1985;139:25-28.

Fanaroff Discussion

Mathews: We would be remiss if we didn't mention another factor, the remarkable retardation of growth that occurs with smoking.[1]

1. Rubin BK. Exposure of children with cystic fibrosis to environmental smoke. N Engl J Med 1990;323:782-788.

Fanaroff: I think that's a point well taken. There is abundant evidence now that children with respiratory disorders are adversely affected by passive smoking. I said we would endorse a nonsmoking environment for the graduates of neonatal and intensive care units.

Goldberg: Can you just comment on the outcome of the 'micronate' (< 750 g). Also, you mentioned that days on mechanical ventilation seems to be an important time cutoff in terms of outcome. Can we assume that if we shortened that time these infants would have a better outcome?

Fanaroff: The numbers on micronates are extremely small and there is inherent bias—most of the survivors have been females, and the follow-up period for these micronates has been short.[1] Overall, there is a handicap rate of one in three. Whether the functional handicap rate is going to be higher remains to be seen. Maureen Hack is coordinating a regional follow-up that includes five centers, so she may be able to get a bit of feel about the follow-up in these micronates. I think that's one of the ethical dilemmas that we have to face. Surprisingly, during the conference that Ron (Goldberg) alluded to, three posters were presented looking at the survival rate of low-birthweight babies;[2] the 50% mark is at about 25 weeks gestation. The second point about the definition of bronchopulmonary dysplasia is one that could result in a very long debate at this meeting. In the manuscript, I presented past definitions—Northway[3] followed by Bancalari[4]—and then suggested that Shennan et al's definition actually makes a lot more sense,[5] particularly as more of these smaller babies survive, mainly on oxygen requirements at a corrected age of 36 weeks gestation. If you look at this data from Toronto, this had a very good predictive value so that if you didn't require oxygen at a corrected age of 36 weeks gestation, there was a 90% chance that there would be a normal outcome. On the other hand, if you still had an oxygen requirement at 36 weeks corrected age, you are looking at handicap rate approaching 60%. This looked like a nice, simple way of sorting out the data.

1. Hack M, Fanaroff AA. Outcomes of extremely low-birth-weight- infants between 1982 and 1988. N Engl J Med 1989;321:1642-1647.
2. Phelps DL, Brown DR, Tung B, et al. 28-day survival rates of 6676 neonates with birth weights of 1250 grams or less. Pediatrics 1991;87:7-17.
3. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. N Engl J Med 1967;276:357-368.
4. Bancalari E, Gerhardt T. Bronchopulmonary dysplasia. Pediatr Clin North Am 1986;33:1-23.
5. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: Prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-532.

Hazinski: Isn't oxygen dependence just a marker for babies with severe disease and lower birthweight? How can you adjust for that factor? Let me ask a general question: How do you assess the importance of one factor, when it's so closely linked to another factor? These data ought to be susceptible to multiple linear-regression and logistic-regression models.

Fanaroff: Tom (Hazinski), you are assuming that there is a good database, and I think the major problem is that there is a very limited database. If there were a database, I think you would be able to perform these different kinds of analysis that you're calling for. I think our database is very crude and that's why we are, at the moment, just 'lumpers.' You are absolutely right, there are so many variables—if you're ventilator-dependent, you have a much greater chance of becoming infected because you're going to have all sorts of invasive procedures done to you. So, I think that the follow-up process is at a very crude stage, and we need to extend the data.

Barnes: What are some of the answers? Do you think a national registry with a better described population and more definition would be valuable? I noticed you said conventional ventilation vs high frequency, but there wasn't much breakdown on the type of conven-

tional ventilation vs the type of high-frequency ventilation that was used—kind of broad categories.

Fanaroff: A national registry would be fine as long as we are all talking about uniform definitions. In the data that I showed, the only controlled trial is the HIFI study.[1,2] In other studies, you may get the initial reports, the survival data, how many bled through their head, and how many had air leaks, but there may be no other data of any consequence.

1. Rigatto H, Davi M, Frantz ID III, et al. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 1989;320:88-93.

2. Rigatto H, Davi M, Frantz ID III, et al. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: Neurodevelopmental status at 16 to 24 months of postterm age. J Pediatr 1990;117:939-945.

Respiratory Care in the Transport of Critically Ill and Injured Infants and Children

John W Salyer RRT

Introduction

The transport of sick and injured pediatric and neonatal patients involves many disciplines within the health-care community. Reasons for transport and transport systems described in the literature are shown in Table 1. In this paper I discuss aspects of respiratory care pertinent to interhospital transport.

The number of agencies providing interhospital transportation for sick and injured infants and children appears to have grown prodigiously over the last 20 years—probably due largely to the increasing concentration of specialized resources in regional centers. Considerable evidence suggests that skilled, rapid transport to specialized care facilities results in improved outcome.[1-5]

History

Means of transporting the ill and injured have been described for more than two millenia. The Gospel according to the physician Luke (5:18-19) reveals:

> And behold, men brought in a bed a man which was taken with a palsy: And they sought means to bring him in and to lay him before Him (Jesus). And when they could not find by what way they might bring him in because of the multitude, they went upon the housetop, and let him down through the tiling with his couch into the midst before Jesus.

Thus, they had transported this patient that he might receive healing.

Table 1. Reasons and Services for Transporting Sick and Injured Patients

Reasons To Transport
Primary transport—transport from the scene of accident or injury to a health care facility
Secondary transport—interhospital transport for the provision of specialized services not available at referring facility (eg, specialized trauma or critical care)
Back transport—transport back to the referring facility when specialized services are no longer needed or in the event that the patient has died
Interhospital transport for economic reasons (from private to publicly funded facilities)
Intrahospital transport to areas of the hospital where special services can be performed (eg, surgical and diagnostic procedures)
Types of Transport Services
Publicly operated emergency medical services (EMS), such as fire-department rescue squads composed of paramedics and emergency medical technicians
Privately operated ambulance companies
Hospital-based transportation services (often called mobile intensive care services)

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Abbreviations Used in This Paper

AAP	—American Academy of Pediatrics
ACLS	—Advanced cardiac life support
BP	—Blood pressure
EMI	—Electromagnetic interference
ETT	—Endotracheal tube
FAA	—Federal Aviation Administration
F_{IO_2}	—Fractional inspired oxygen concentration
ICU	—Intensive care unit
NICU	—Neonatal intensive care unit
NRP	—Neonatal Resuscitation Program
PALS	—Pediatric advanced life support
P_{aCO_2}	—Arterial carbon-dioxide tension
P_{etCO_2}	—End-tidal carbon-dioxide tension
PICU	—Pediatric intensive care unit
P_{IO_2}	—Inspired oxygen tension
RCP	—Respiratory care practitioner

Through the centuries, many vehicles and devices have been described for the transporting of patients to hospitals—litters, sedans, carts, wagons, coaches, post-chaises, gigs, flys, and cabs. In the 19th century, hospitals in metropolitan London recognized the importance of getting patients to their facilities and modified their admission-day scheduling practices to make it easier for patients to utilize public transportation.[6]

Important advances in the care and transportation of injured patients have resulted from that most dismal of human enterprises, war.[7,8] In the 18th century, the Duke of Marbrough arranged for soldiers wounded during the Battle of Blenheim to be transported to the hospital "by all available wagons from the surrounding countryside."[1] It has been reported[1,9] that the Franco-Prussian War (1870) saw the beginning of air transport when hot-air balloons were used to evacuate 160 of the wounded from the siege of Paris; however, this contention has been disputed.[10]

The wars of this century have led to tremendous advances in rapid transport from battlefield to medical facility.[11] One of the first reports of the use of heavier-than-air craft described the transport of 12 casualties from a battlefield in Serbia by the French in 1915. World War II saw the widespread use of aircraft to transport the injured, and by 1945 the U.S. Army's air evacuation system had transported 454,000 patients.[12]

Advances in military transport and care of the injured have affected battlefield mortality. During the Civil War, 75% of the Union Army's wounded soldiers survived,[7] whereas during the Vietnam War 97.5% of those who reached a U.S. medical facility survived.[8]

The experience gained by the military has helped to shape civilian transport and care. I believe that the most important result has been the development of regional centers for the specialized care of critically ill and injured pediatric and neonatal patients.[2-4,9,13-22]

Utilization of Pediatric and Neonatal Transportation Services

It is difficult to determine how many neonatal and pediatric patients are transported each year in in the United States. To my knowledge, no comprehensive statistics on national patterns of transport services exist. However some regional reports are described in Table 2.[2,4,5,9,14,19,20,23]

The development of tertiary care centers has been an important proving ground for transport techniques. Commonly, these centers are university-affiliated and have special transport teams composed of neonatal intensive care unit (ICU) personnel. This type of service has been shown to be more effective in reducing mortality than have transport teams not specially trained.[22,24,25]

At Rainbow Babies and Childrens Hospital (a university-based pediatric teaching hospital in Cleveland, Ohio), 44% of transported patients go directly to an ICU (about one third to the 16-bed pediatric ICU, or PICU; and two thirds to the 38-bed neonatal ICU, or NICU). Rainbow's utilization of pediatric transport during 1988 and 1989 is shown in Table 3.

The desirability of transporting the high-risk mother to a tertiary care center before delivery versus possible postnatal transport of the infant is frequently discussed. The transport of critically ill, low-birthweight infants is a difficult and potentially risky undertaking. Some reports have concluded that neonatal mortality is significantly higher with postnatal transport than with antenatal transport.[15,22,26] Other investigators have argued that

Table 2. Characteristics of Pediatric Transport Services

Area	No. of Patients	Length of Study	Age of Patients	Mode of Transport	% of Patients Intubated	RCP Used on Selected Transports
Melbourne, Australia[5]	46	11 mo 1979-1980	1 mo-17 y	Air 57% Ground 43%	39%	No
Denver, Colorado[9]	342	6 mo 1979-1980	1 mo-18 y	Air 38% Ground 62%	50%	Yes
Columbus, Ohio[20]	21	7 mo 1971	Birth-18 y	Air 100%	?	No
Birmingham, Alabama[2]	117	24 mo 1986-1988	Birth-15 y	Air 54% Ground 46%	68%	Yes
Stanford, California[23]	115	24 mo 1978-1979	2 wk-18 y	Ground 100%	39%	Yes
Salt Lake City, Utah[19]	752	32 mo 1979-1981	3 wk-16 y	Air 95% Ground 5%	?	No
Adelaide, South Australia[14]	379	108 mo 1974-1983	Birth-18 y	Air 68% Ground 32%	25%	No
Melbourne, Australia[4]	158	36 mo	?	Air 46% Ground 54%	59%	No

comparing outcome solely on the basis of delivery site is inappropriate because of the many confounding variables—most notably that infants selected for antenatal and postnatal transfer represent different populations.[16,27]

Debate aside, antenatal transport is increasing in some parts of the country, thus reducing the number of neonates transferred.[28] If this trend continues, the demand for respiratory care practitioners (RCPs) in neonatal transfers may decline. However, the need will not disappear because many premature deliveries are precipitous, many infants are not deemed at risk before delivery, and many economically disadvantaged mothers do not receive prenatal care and, thus, will not be transported before delivery.

The current system of regional tertiary neonatal centers and neonatal transport services has led to overcrowding in some NICUs.[29] The pressure to vacate NICU beds and the cost of providing neonatal intensive care have led to the practice of "back-transporting" recovering neonates to their original community hospitals.[29,30] This practice also allows infants to be placed in facilities closer to their parents' homes. Because many of these patients require oxygen therapy or mechanical ventilation, RCPs commonly participate in their transport.

National statistics comparing ground and air transport of infants and children are not currently available. However, the utilization of air transport services is becoming increasingly widespread. At least 246 air transport services are in operation in the U.S. (1990).[31] From 1972-1988, 655,000 patients were transported by helicopter.[32] In 1988 alone, at least 120,900 patients were transported by medical helicopters (nearly 15 million mission-miles flown), and 18,700 patients were transported by fixed-wing aircraft.[32]

Team Composition

The services used to transfer pediatric and neonatal patients to tertiary centers must be an extension of the critical care services at the tertiary center.[23,33] Crone has stated:[34]

> The major objective of intensive care for infants and children is to provide maximum surveillance and support of organ systems during acute, but reversible, life-threatening illness.

Table 3. Utilization of Transport Services and Patient Characteristics: Rainbow Babies and Childrens Hospital, Cleveland

Number of Patients	1988	1989	Total
Transported	1,368	1,277	2,645
On supplemental oxygen	678	586	1,264
Intubated	293	236	529
By ground transport	1,288	1,188	2,476
By air transport	101	96	197
Taken directly to NICU	360	390	750
Taken directly to PICU	252	179	431
Patient Ages			
Newborn-1 year	784	762	1,546
1-5 years	334	252	586
6-10 years	108	95	203
11-15 years	68	59	127
⩾ 16 years	29	24	53
Unknown	66	92	158
Transport Distance			
1-40 miles	610	682	1,292
41-80 miles	123	134	257
81-120 miles	80	77	157
⩾ 121 miles	57	71	128
Unknown	497	320	817
Average transport time (min)	125	131	—

This also should be the objective of the transport service. To achieve this requires that specially trained personnel, intimately familiar with neonatal and pediatric critical care, make up the transport team.[35]

The issue of who should make up the transport team is controversial,[1] and one specific combination does not appear applicable to every institution and every situation:[36] Personnel combinations for existing transport teams include two nurses; a nurse and an emergency medical technician; a nurse and a physician; a nurse and an RCP; a physician and an RCP; and a nurse, physician, and an RCP.

The transport team must be composed of persons who (1) possess considerable pediatric and neonatal critical care experience,[35] (2) are rigorously trained in the skill needed,[1,35,37-42] and (3) participate in transport frequently enough to maintain a high level of expertise.[35]

Those caring for pediatric and neonatal patients need special training and extensive experience as Crone has stated:[34]

> Although principles of intensive care for infants and children are similar to those for adult intensive care, the age spectrum from infancy through adolescence requires that the the intensive care staff have special expertise.

I would add that expertise in airway and ventilator management is a necessity. Because the transport service is an extension of the ICU, it must have the same capabilities.

Harris[38] observed that emergency cardiac care performed in a helicopter by ACLS-trained personnel without flight experience was substandard as opposed to adequate care performed by fulltime flight transport personnel, and suggested that hospital-based helicopter services be staffed only with fulltime crew members extensively trained and provided with sufficient opportunity to maintain their skills.

It is my conviction that some air transport services do not perform enough pediatric and neonatal transports to become and remain skilled. Therefore, such services need to supplement their regular crews with specially trained and experienced practitioners.

Some transport services have developed separate teams for adult and pediatric-neonatal transport composed of specially trained nurses and emergency medical technicians. In addition, RCPs (and sometimes resident physicians and additional nurses) are sometimes pulled from ICUs for neonatal and pediatric transports. The senior pediatric house officer may act as team coordinator and determine the team makeup for a specific transport. An RCP will usually be a part of the team if an intubated patient is to be transported, if intubation is anticipated, or if respiratory instability is suspected.[9] In one study,[43] 45% of all patients transported required the services of an RCP. In a series of neonatal patients transported in France, 40% required intubation.[44]

Although duties may vary, the RCP is an established member of many neonatal and pediatric transport teams,[1,9,16,23,24,35,36,39,40,42,43,45-49] and duties include (1) assembling and checking respiratory

equipment, (2) assessing the patient's respiratory condition, (3) managing the airway, (4) administering oxygen or managing the ventilator, (5) monitoring the patient's respiratory status, and (6) assisting other team members as needed. Teams lacking an RCP invariably have another team member skilled in airway management and mechanical ventilation.[50,51]

In a recent survey,[39] 50% of responding services indicated that RCPs are involved in their transports of critically ill infants. In another survey (323 pediatric and/or neonatal special care facilities),[49] 55% included an RCP on the transport team.

The requisite training for team members (including RCPs) has been described by the American Academy of Pediatrics (AAP):[35]

> All transport team members should complete a planned formal training program approved by the medical director and supplemented by inservice practical training. The course should be of sufficient duration and content to cover all responsibilities related to the care and monitoring of pediatric patients during transport, technical skills required for emergency management, operation of transport equipment, adaptation to the physical environment of transport vehicle, and physiologic consequences of the transport on the patient.

The Guidelines mandate that RCPs have at least 1 year of experience in pediatric critical care. I further submit that RCPs engaging in transport should be certified in the AAP's Pediatric Advanced Life Support (PALS) and the American Heart Association's Neonatal Resuscitation Program (NRP).

The AAP has also recommended that transport RCPs be registered (RRT) or registry-eligible respiratory therapists. Some department managers may find this nearly impossible to comply with. In a recent survey,[49] 62% of responding pediatric hospitals reported that fewer than one half of their RCPs are registered. How many of those not registered are registry eligible is unknown.

One controversy related to team composition centers on whether a physician should be included. Some insist that a physician be present if the need for intensive care is anticipated.[23] Others have concluded that a physician may not always be necessary.[48] Resolution of the controversy probably depends on whether one believes that the severity of the patient's condition can be accurately predicted prior to team departure. Critically ill patients may require the services of a trained intensivist to lead the transport team. I have observed that information received by phone can be inaccurate, making it difficult to predict whether a physician will be needed. Although many patients can be safely transported without a physician, it would seem prudent to make errors in team selection on the the side of caution. If doubts exist, a qualified physician should be included on the team.

Some centers utilize a transport team composed of an RCP and a nurse for sick neonates, and only add a physician when older pediatric patients are involved.[42] In a survey reported by McCloskey and Johnston,[39] 72% of responding pediatric transport services indicated that a physician is always included.

Transport physicians should be trained in critical care and be capable of intubating, placing chest tubes, managing fluid therapy, and directing cardiopulmonary resuscitation efforts.[9,25,33,35,40] I believe that a knowledge of ventilatory support equipment is also necessary unless an adequately trained RCP is a member of the team. I have noted that some centers send incompletely trained second-year house officers on transport.

The use of properly trained personnel and appropriate equipment makes a duplication of the experience of Srikasibhandha and Cats less likely:[52] When untrained personnel were used to transport neonates to a regional center in Holland, several patients died en route.

Transport Equipment

Table 4 is a list of equipment and supplies needed to provide respiratory care during transport. A large canvas bag or other container that allows logical organization and easy retrieval should be used for respiratory supplies, and all team members should be familiar with the supply system.

The inside of a moving ambulance or the cabin of an aircraft in flight (particularly a helicopter) is a hostile working environment, and the sick

Table 4. Equipment and Supplies Needed To Provide Respiratory Care during Neonatal and Pediatric Transport

Equipment	Supplies
Adequate supply of oxygen and compressed air	Resuscitation masks (sizes 0, 1, 2, 3, 4)
Air-oxygen blender	Feeding tubes (size 6, 8, and 10 Fr)
Mechanical ventilator with circuit	Disposable oxygen hood
Manual resuscitator capable of giving 100% O_2 with PEEP	Oxygen connecting tubing
Noninvasive oxygen monitor (S_{pO_2} or P_{tcO_2})	Disposable hand-held nebulizer with tubing (for bronchodilators)
Oxygen analyzer	Cloth adhesive tape for taping endotracheal tubes (½" & 1")
Airway pressure monitor (electronic or mechanical)	Tincture of benzoin for taping endotracheal tubes
Electrocardiograph monitor	Pulse oximeter probes (at least two, in case one fails)
Portable suction apparatus	Endotracheal tubes (sizes 2.5-7.0)
Laryngoscope handle	Stylette
Laryngoscope blades (sizes newborn to adult)	Forceps
Extra laryngoscope bulbs and batteries	Suction apparatus
Stethoscope	
Tools	

newborn can be as unstable a patient as one is likely to encounter.[53] All planning and preparation for transport should be made in that light.

The RCP must ensure an adequate supply of medical gases for the transport vehicle before leaving the transport center. In addition to being a horrifying experience, I believe that running out of oxygen while transporting a patient is unconscionable. Because things can go wrong and cause delay, it is prudent to take at least twice the amount of oxygen actually thought to be needed.[53]. The potential for disaster has been well described by Clews:[45]

> One of the most frightening things I have experienced, in my clinical practice as a transport team nurse occurred when a 2-year-old had a cardiac arrest in the back of an ambulance during rush hour traffic on an inner-city expressway ... Unfortunately, this critical event was further complicated by a mechanical failure of the ambulance's lights and sirens.

My own experience confirms the need to ensure an adequate oxygen supply—witness a recent trip that lasted 66% longer than anticipated. Anticipating the amount of oxygen that will be needed can be difficult. The RCP must take into account all sources of gas consumption. Some commonly used air-oxygen blenders have a continuous bleed in addition to the flowrate set on the flowmeter. For example, the Bird 3800 Microblender bleeds 10-12 L/min and the Bird HI/LO blender has a bleed rate of 12-14 L/min (Bird Products, Palm Springs CA). So, the HI/LO on the low-flow setting with the auxiliary flow turned on and the flowmeter set at 10 L/min consumes 24 L/min.

Some pneumatically powered, fluidically controlled transport ventilators have an internal gas consumption in addition to the set flowrate. The Bio-Med MVP-10 (Bio-Med Devices Inc, Madison CT) is one such ventilator, but the manufacturer has wisely included a chart of estimated total gas consumption based on ventilator settings. At a frequency of 50 breaths/min this ventilator has an internal gas consumption of about 4 L/min.[54] Table 5 lists ventilators suitable for neonatal and pediatric transport, with some of their performance specifications.[55]

Essential tools to be taken on every transport include a cylinder key (wrench), screwdriver, pliers, scissors, hemostats, and a small flashlight. Repairs may be necessary en route.

Plans should be made and implemented for dealing with equipment failure during transport. Redundant systems should be designed and implemented. If the manual resuscitator malfunc-

Table 5. Ventilators That Can Be Used for Neonatal and Pediatric Transport

Manufacturer	Air Shields	Bear Medical Systems Inc	Bio-Med Devices Inc	Bird Products Corp	Infrasonics Inc	Newport Medical Instruments Inc	Seehrist Industries Inc	Siemens-Elema Ventilator Systems	SLE Ltd
Model	—	BP-2001	MVP-10	8901	Infant Star	E1001	IV-100B	900C	Newborn 250
Dimensions (cm)	—	36 × 26 × 26	23 × 21 × 8	35 × 30 × 19	38 × 33 × 28	27 × 24 × 17	36 × 33 × 23	50 × 32 × 23	31 × 23 × 20
Weight (kg)	—	12.2	2.3	6.8	16.5	5.9	7.2	8.1	10
Expiratory time range (s)	—	0.25-3	0.25-2.5	—	0.2-5	—	0.3-60	—	—
F_{IO_2} range (%)	—	21-100	21-100	21-100	21-100	21-100	21-100	21-100	21-100
Flow range (L/min)	—	3-30	0-36	3-30	4-40	0-72	0-40	0.5-40	1-50
Inspiratory time range (s)	—	0.1-3	0.2-2	0.1-2.5	0.1-3	0.1-3	0.1-2.9	—	0.001-180
Safety pressure pop-off valves: Function range (cm H_2O)	—	10-72	0-120	15-80	0-90	0-100	25	16-120	20-80
Warranty	—	—	1 year	1 year	1 year	1 year	—	2 years	1 year
Stationary/transport	—	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—
Pediatric applications	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rate capability	Yes	—	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Expiratory pressure capability	—	—	Yes	—	Yes	Yes	Yes	Yes	—
Manual operation	—	—	—	Yes	Yes	Yes	Yes	Yes	Yes
Modes of operation:									
CPAP	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
IMV	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Controlled ventilation	Yes	Yes	Yes	Yes	—	Yes	Yes	Yes	Yes
Safety systems:									
External	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Internal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Displays:									
Actual I:E	Yes	Yes	—	Yes	Yes	—	Yes	—	Yes
Actual rate	Yes	Yes	—	Yes	Yes	—	Yes	Yes	Yes
Expiratory time	—	Yes	—	Yes	Yes	—	Yes	—	Yes
Inspiratory time	—	Yes	—	Yes	Yes	—	Yes	—	Yes
Inspired O_2	—	—	—	—	—	—	—	—	Yes
Peak pressure	—	—	—	Yes	Yes	—	—	—	Yes
Mean airway pressure	—	—	—	Yes	Yes	—	—	—	Yes

Modified, with permission, from Reference 55.

tions, a replacement must be instantly available. If the incubator heater fails, chemical heating packets must be ready for use. In a series reported by Kanter and Tompkins,[56] equipment-related adverse events occurred in 12 of 117 pediatric transports. When checking equipment in preparation for transport, the RCP should ask What will I do if this piece of equipment fails?

Electromagnetic interference, or EMI, (analogous to the interference one may see on a television screen when an electric drill is operated nearby) can be generated by transport equipment,[57] and has the potential for affecting the performance of avionics equipment and, thus, aircraft operation. Nish et al[57] tested the amount of EMI emitted by more than 20 neonatal monitors, incubators, and ventilators, and found that about 70% of the equipment tested failed U.S. Air Force test standards for EMI. They concluded that, although no aircraft accidents are known to be the result of EMI, the potential for catastrophe exists. They suggest that transport equipment should not be purchased if it does not meet U.S. Air Force EMI standards; however, Nish et al admit that military EMI standards may be too strict for civilian purposes. I agree with their suggestion that the Federal Aviation Administration (FAA) should develop EMI standards for civilian transport equipment as soon as possible.

Care must be taken to adequately secure all equipment to prevent its falling during transport. As Clews writes:[45]

> One transport nurse who had been involved in an accident described it as being very much like the movie Poseidon Adventure—things were flying everywhere.

Finally, aircraft cabins are temperature controlled, but clothing suitable for the outdoor climate should be readily available. If an aircraft is forced down in a remote area during cold weather, transport crews may be exposed to the elements for some time. The thought of such exposure in hospital 'scrubs' is sobering.

Patient Assessment, Stabilization, and Monitoring

Assessment of the patient's condition begins even before the team leaves the transport center. The importance of good communication cannot be overemphasized.[58,59] Britten and Rogers,[1] specify the patient information required to initiate transport: (1) age, weight, and name; (2) general condition and appearance; (3) vital signs; (4) major medical problems; and (5) course of events leading to present status. To this list I would add the most recent arterial blood gas values and the extent of respiratory care the patient is receiving. The ideal communication system allows the transport team (while en route) to continuously discuss the patient's condition with both the referring and receiving hospitals.[1]

Patient stabilization prior to transport is probably the most critical aspect of interhospital care because it can minimize subsequent deterioration in an environment that may not permit detection or treatment of problems.[46] Immediately upon arrival at the referring hospital, the transport team should assess the patient's physical condition—ensuring proper airway management, adequate ventilation, and adequate circulation. The protocols described in PALS[60] are an excellent guide. First, a patent airway must be verified or established. If respiratory deterioration appears imminent or likely to occur during transport, intubation should be performed and ventilatory support with 100% oxygen instituted as soon as possible.

In most acute respiratory emergencies (with occasional exceptions), high oxygen concentrations can be delivered without harmful effects.[60] Pediatric patients with chronically elevated P_{aCO_2} (eg, cystic fibrosis and bronchopulmonary dysplasia) may have their respiratory drive abolished if high oxygen concentrations are administered, and low-birthweight neonates are at greater risk than term babies for developing retinopathy of prematurity if hyperoxemia is allowed to persist. However, these concerns should not overshadow the need to achieve acceptable oxygenation in the critically ill, but should instead cause the clinician to cautiously titrate the oxygen concentration in these patients once cardiorespiratory stability has been established.

I believe that the temptation to delay intubation until after transport in patients who appear to have only marginal respiratory difficulties should be resisted. Intubation of a small child or neonate in a moving ambulance or aircraft cabin is difficult and should be avoided if possible. Some authors

have suggested that the transport vehicle be stopped if intubation becomes necessary.[36]

Securely affixing the endotracheal tube (ETT) to the patient's face is essential to decrease the likelihood of accidental extubation.[56] Accidental extubation does occur,[61,62] and the smaller the patient the greater the likelihood of it occurring. Reintubation is especially difficult to perform in a helicopter cabin. Although various taping techniques have been reported, some evidence suggests that the use of elastic tape and tincture of benzoin is a superior method.[62,63] However, excellent taping technique alone cannot ensure that accidental extubation will not occur. Manual stabilization of ETTs by transport staff may be necessary to further reduce movement of even well-taped tubes.[56] The use of extremity restraints in active patients is essential and, although controversial, sedation or paralysis may also be necessary.[64]

Venous access must be established prior to transport.[65] If attempts to gain venous access are unsuccessful, intraosseous infusion can be a rapid and safe alternative.[66-68] Hypovolemic shock is common in pediatric patients who require emergency care,[60] and volume expansion may be required.

The patient assessment includes evaluation of temperature, blood pressure, heart rate, respiratory rate and status, color, and radiographic and laboratory results (eg, hematocrit, glucose, and arterial blood gas and pH values).

If the patient is intubated, ETT position should be confirmed by radiograph, and the adequacy of spontaneous breathing or ventilatory support be confirmed by blood gas analysis prior to departure. If noninvasive respiratory monitors (eg, transcutaneous P_{O_2}/P_{CO_2}) are to be used during transport, their agreement with blood gas values should be established.

The noise level in transport vehicles can make auscultation of breath sounds to confirm ETT placement nearly impossible. The noise level in most helicopters (> 100 dB) makes even ordinary conversation impossible.[53,69] An in-vitro study conducted in a helicopter (Model MBB BO-105) revealed that flight nurses were, without exception, unable to hear simulated breath sounds using either conventional or amplified stethoscopes.[70] In my experience, auscultation is often impossible even during ground transport. Campbell et al[71] found that the sound levels during ground transport could reach 101 dB, which is comparable to that measured in some fixed-wing aircraft. The AAP[47] has recommended that aircraft-cabin noise levels be kept below 85 dB, but it is difficult to determine the extent to which this recommendation is (and can be) complied with.

Vibration can be a concern during transport in rotary-wing aircraft and in some ground ambulances. Bouncing can be so exaggerated that it may make it almost impossible to discern chest-wall excursion and thus to assess the adequacy of ventilation.

An alternative method of assessing ETT position is to use a colorimetric end-tidal CO_2 detector, a small, disposable device that changes color in response to changes in CO_2 concentration (Fenem, New York NY) and is placed between the ETT and the ventilator circuit. If the tube becomes dislodged from the trachea and slips into the esophagus, the concentration of CO_2 in the ETT drops, and thus the detector does not exhibit the expected tidal color change. When the device was tested during 100 emergency intubations (ground, air, and emergency department), all tracheal (98) and esophageal (2) intubations were correctly identified.[72] Of the 100 patients involved, 35 experienced cardiac arrest (all were tracheally intubated), and no colorimetric changes were noted during cardiopulmonary resuscitation in 31% (11) of these 35 patients. Of 11 patients in whom colorometric changes were not noted, none were successfully resuscitated. Although Higgins et al[73] have reported on the measurement of end-tidal CO_2 concentrations for assessing the adequacy of cardiopulmonary resuscitation, Ours et al[74] reported that they found the disposable end-tidal CO_2 detector reliable in identifying intubation in only 86% of cases.

Adequate humidification of gases delivered through the ETT is no less important during transport than at any other time. The risk of ETT occlusion by inspissated secretions is real,[56] and is increased as tube size decreases.[5] A cold humidifier may not add sufficient moisture to prevent inspissation and possible mucosal damage. A heated humidifier can be used during transport, but the equipment is bulky and adds a considerable power drain to battery

systems. Coleman[75] has described a heated transport incubator with a disposable humidifier placed in the ventilator circuit. The water and chamber are kept inside the incubator (even during warmup) and thus are able to heat and humidify the inspired gas.

The use of heat and moisture exchangers (hygroscopic condensers) has been reported,[5] but I do not believe that neonatal-pediatric applications have been adequately studied.

Morbidity and mortality in small, premature infants is related to cold stress, with mortality increasing with each degree of temperature loss.[46] Transport incubators should be prewarmed, have fully charged battery packs, and be capable of maintaining the patient's normal physiologic temperature. I believe that it is prudent to carry extra battery packs for the incubator.

Noninvasive Respiratory Monitoring during Transport

Because noise interferes with auscultation of breath sounds and, thus, the determination of proper ETT position and the adequacy of ventilation, noninvasive monitoring—pulse oximetry,[1,42,76-79] transcutaneous monitoring,[40-42] and end-tidal CO_2 monitoring[36,80,81]—appears to have become a standard of care during pediatric and neonatal transport.

Although substantiating data are unavailable, I believe that pulse oximetry is probably the most widely used of these. However, Ross and Renzi[82] observed in 49 patients transported by air that pulse oximeter use neither affected initial airway management nor detected occult hypoxemia. I believe that the utility of the pulse oximeter is not in guiding initial treatment but in providing ongoing monitoring in the adverse transport environment.

Pulse oximetry has been tested in a number of populations and has generally been found to be adequately accurate (±2-3%) and precise.[83] However, inaccuracy is greater with elevated levels of dyshemoglobins and profound hypoxemia.[83] Sensitivity to motion artifact may also be a serious limitation.[84] In addition, the clinician must not assume that the pulse oximeter necessarily reflects overall oxygen delivery. The interested reader is referred to a more detailed description.[84]

Pekka et al described a technique for assessing blood pressure (BP) in aircraft cabins:[85]

> To measure systolic BP with the pulse oximeter we used the real-time plethysmographic waveform. The BP cuff was applied in the usual fashion on the upper arm and the pulse-oximeter probe was applied to the ipsilateral finger. The cuff was inflated above the systolic BP, which was indicated by the disappearance of the plethysmographic waveform. As the cuff was slowly deflated (2-3 torr/s) the pulse waveform reappeared. The pressure at which the waveform reappeared was recorded.

Talke et al suggest that results by this method correlate well with conventional methods.[86] This study was done in adult patients but should be suitable for pediatric patients.

Transcutaneous monitoring may have two advantages over pulse oximetry: (1) the combined O_2-CO_2 electrode monitors ventilation and oxygenation and (2) the device is probably less sensitive to motion artifact.

End-tidal gas monitoring during transport has not been widely reported,[36] but may have utility. In patients without lung disease or serious ventilation-perfusion disturbances, peak values of P_{etCO_2} generally agree well with P_{aCO_2} measurements (gradient < 2-3 torr),[87] but in the transport population utility may be reduced.[88] The use of capnometry in pediatric and neonatal patients needs to be further examined.

Concerns about the Effects of Altitude

During transport by helicopter and fixed-wing aircraft, the RCP must be aware of the physiologic effects of increasing altitude. As the barometric pressure falls with increasing altitude, two things happen: the free gas in body cavities expands and the ratio of inspired oxygen tension to fractional inspired oxygen concentration (P_{IO_2}/F_{IO_2}) decreases (Table 6).[89] Air in the pleural space (pneumothorax) and air in the stomach must be evacuated via chest and orogastric tube and F_{IO_2} must be increased appropriately to maintain P_{IO_2} and to ensure adequate oxygenation of the patient.

In Conclusion

Providing respiratory care for critically ill infants and children during interhospital transport is an

Table 6. Effect of Altitude on Inspired Oxygen Tension

Altitude (ft)	Altitude (m)	Barometric Pressure (torr)	Barometric Pressure (kPa)	Inspired Oxygen Tension (torr)	Inspired Oxygen Tension (kPa)	Equivalent F_{IO_2}*
0	0	760	101	149	20	0.21
1000	305	733	97	143	19	0.2
2000	610	707	94	138	18	0.19
3000	914	681	91	133	18	0.19
4000	1219	656	87	127	17	0.18
5000	1524	632	84	122	16	0.17
6000	1829	609	81	117	16	0.16
8000	2438	564	75	108	14	0.15
10000	3048	523	70	99	13	0.14
12000	3658	483	64	91	12	0.13
14000	4267	446	59	83	11	0.12
16000	4877	412	55	76	10	0.11
18000	5486	379	50	69	9	0.1
20000	6096	349	46	63	8	0.09
22000	6706	321	43	57	8	0.08
24000	7315	294	39	52	7	0.07
26000	7925	270	36	47	6	0.07
28000	8534	247	33	42	6	0.06
30000	9144	226	30	37	5	0.05

* F_{IO_2} at sea level that would produce the same inspired oxygen tension.
Modified from Reference 89, with permission.

exacting task that requires highly trained and experienced personnel and well-chosen, properly functioning equipment; however, improved patient outcome can be the rewarding result.

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REFERENCES

1. Britten AG, Rogers MC. Transportation of critically ill children. In: Rogers MC, ed. Textbook of pediatric intensive care. Baltimore: Williams & Wilkins, 1987:1385-1400.
2. Breaux CW, Smith G, Georgeson KE. The first two years experience with major trauma at a pediatric trauma center. J Trauma 1990;30:37-43.
3. Colombani PM, Buck JR, Dudgeon DL, Miller D, Haller JA. One-year experience in a regional pediatric trauma center. J Pediatr Surg 1985;20:8-13.

4. Duncan AW, Mullins GC, Kent M, Phelan PD. A paediatric emergency transport service: One year's experience. Med J Aust 1981;2:673-676.
5. Owen J, Duncan AW. Towards safer transport of sick and injured children. Anaesth Intensive Care 1983;11:113-117.
6. Hart HW. The conveyance of patients to and from hospitals, 1720-1850. Med Hist 1978;22:397-407.
7. Ramenofsky ML, Luter A, Curreri PW, Talley MA. EMS for pediatrics: Optimum treatment or unnecessary delay. J Pediatr Surg 1983;18:498-504.
8. Boyd DR. Comprehensive regional trauma and emergency medical service delivery systems: A goal of the 1980s. Crit Care Q; Dec 1982:1-21.
9. Dobrin RS, Block B, Gilman JI, Massaro TA. The development of a pediatric emergency transport system. Pediatr Clin North Am 1980;27:633-646.
10. Lam DM. Wings of life and hope: A history of aeromedical evacuation. Problems Crit Care 1990;4:477-494.
11. Fisher GW. Acute arterial injuries treated by the U.S. Army medical service in Vietnam. J Trauma 1967;7:844-852.
12. Merwin CA. U.S. Air Force patient airlift from balloons to high speed jets. J Air Med Transport 1990;9:18-22.
13. Haller JA, Shorter M, Miller D, Colombani P, Hall J, Buck J. Organization and function of a regional pediatric trauma center: Does a system of management improve outcome? J Trauma 1983;23:691-696.
14. Sweeny DB, Turtle MJ. Paediatric retrievals in south Australia. Anaesth Intensive Care 1985;13:410-414.
15. Kollee LAA, Verloove-Vanhorick PP, Verwey RA, Brand R, Ruys JH. Maternal and neonatal transport: Results of a national collaborative survey of preterm and very low birth weight infants in the Netherlands. Obstet Gynecol 1988;72:729-732.
16. Delaney-Blacks V, Lubchenco LO, Butterfield LJ, Goldson E, Koops BL, Lazotte DC. Outcome of very-low-birth-weight infants: Are populations of neonates inherently different after antenatal versus neonatal referral? Am J Obstet Gynecol 1989;160:545-552.
17. Fallon MJ, Copass M. Southeast Alaska to Seattle emergency medical air transports: Demographics, stabilization, and outcomes. Ann Emerg Med 1990;19:914-921.
18. Ohlsson A, Fohlin L. Reproductive medical care in Sweden and the Province of Ontario, Canada: A comparative study. Acta Paediatr Scand 1983;306(Suppl):3-15.
19. Black RE, Mayer T, Walker ML, et al. Air transport of pediatric emergency cases. N Engl J Med 1982;307:1465-1468.
20. Haller JA. Toward a comprehensive emergency medical system for children. Pediatrics 1990;86:120-122.
21. Harris BH, Orr RE, Boles ET. Aeromedical transportation for infants and children. J Pediatr Surg 1975;10:719-724.
22. Saule H, Riegel K, Beltinger C. Effectiveness of neonatal transport systems. J Perinat Med 1987;15:515-521.
23. Smith DF, Hackel A. Selection criteria for pediatric critical care transport teams. Crit Care Med 1983;11:10-12.
24. Hood JL, Cross A, Hulka B, Lawson EE. Effectiveness of the neonatal transport team. Crit Care Med 1983;11:419-423.
25. Chance GW, Matthew JD, Gash J, Williams G, Cunningham K. Neonatal transport: A controlled study of skilled assistance. J Pediatr 1978;93:662-668.
26. Kollee LAA, Eskes TKAB, Peer PGM, Koppes JFP. Intra- or extrauterine transport? Comparison of neonatal outcomes using a logistic model. Eur J Obstet Gynecol 1985;20:393-399.
27. Sepkowitz S. Unconvinced of value of antenatal transfer to level 3 intensive care units (letter). Pediatrics 1985;75:801-802.
28. Cowett RM, Coustan DR, Oh W. Effects of maternal transport on admission patterns at a tertiary care center. Am J Obstet Gynecol 1986;154:1098-1100.
29. Bose CL, LaPine TR, Jung AL. Neonatal back-transport. Med Care 1985;23:14-19.
30. Jung AL, Bose CL. Back transport of neonates: Improved efficiency of tertiary nursery bed utilization. Pediatrics 1983;71:918-922.
31. Air transport program directory. J Air Med Transport 1990;9:36-41.
32. Annual transport statistics. Hosp Aviation 1989;8:3.
33. Kissoon N, Grewen TC, Kronick JB, Mohammed A. The child requiring transport: Lessons and implications for the pediatric emergency physician. Pediatr Emerg Care 1988;4:1-4.
34. Crone RK. Paediatric and neonatal intensive care. Can J Anaesth 1988;35:S30-S33.
35. American Academy of Pediatrics committee on hospital care: Guidelines for air and ground transportation of pediatric patients. Pediatrics 1986;78:943-950.
36. Donn SM, Faix RG, Gates MR. Neonatal transport. Current Problems in Pediatr 1985;15(4):1-65.
37. Pettett G, Merenstein GB, Battaglia FC, Butterfield LJ, Efird R. An analysis of air transport results in the sick newborn infant: Part 1. The transport team. Pediatrics 1975;55:774-782.
38. Harris BH. Performance of aeromedical crewmembers: Training or experience? Am J Emerg Med 1986;4:409-411.
39. McCloskey KA, Johnston C. Pediatric critical care transport survey: Team composition and training, mobilization time, and mode of transportation. Pediatr Emerg Care 1990;6:1-3.
40. Merenstein GB, Pettett G. Transport of ventilated infants. In: Goldsmith JP, Karotkin EH, eds. Assisted ventilation of the neonate. Philadelphia: WB Saunders, 1988:376-396.
41. Webster H, Wirth D. Life flight. Pediatr Nurs 1983;10:17-20.
42. Ray LR, Cunningham W. Transport. In: Koff PB, Eitzman DV, Neu J, eds. Neonatal and pediatric respiratory care. St Louis: CV Mosby, 1988:318-331.

43. Smith D, Hackel A. Staffing requirements for pediatric critical care transport teams (abstract). Crit Care Med 1981;9:289.
44. Herve C, Gaillard M, Desfemmes C, Huguenard P. Neonatal distress: Interest of early medical care and medicalized transport. Acta Anaesthesiol Belgica 1984; 35(Suppl):145-151.
45. Clews DL. Interhospital transport of the critically ill child. Holistic Nurs Pract 1989;4:24-29.
46. Mir NA, Javied S. Transport of sick neonates: Practical considerations. Indian Pediatri 1989;26:755-764.
47. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 2nd ed. Elk Grove IL: American Academy of Pediatrics, 1988:210-222.
48. McCloskey KA, King WD, Byron L. Pediatric critical care transport: Is a physician always needed on the team? Ann Emerg Med 1989;18:247-249.
49. Salyer JW, Chatburn RL. Patterns of practice in pediatric respiratory care. Respir Care 1990;35:879-888.
50. Rhee KJ, O'Malley RJ. The effect of an airway algorithm on flight nurse behavior (abstract). J Air Med Transport 1990;9:6-8.
51. Hopkins D, Evans B. A program for certification in airway management and intubation for pediatric transport nurses and respiratory therapists (abstract). J Air Med Transport 1989;8:63.
52. Srikasibhandha S, Cats BP. Transport of the newborn. Z Geburtshilfe Perinatol 1977;181:460-464.
53. Harris BH, Belcher JW. Equipment and planning for neonatal air transport. Med Instrum 1982;16:253-255.
54. MVP-10 Pediatric/neonatal ventilator instruction manual. Madison CT: Bio-Med Devices Inc, 1986.
55. Perinatology/neonatology buyer's guide. Santa Monica CA: Barrington Publications, 1987:24.
56. Kanter RK, Tompkins JM. Adverse events during interhospital transport: Physiologic deterioration associated with pretransport severity of illness. Pediatrics 1989;84:43-48.
57. Nish WA, Walsh WF, Swedenburg M. Effect of electromagnetic interference by neonatal transport equipment on aircraft operation. Aviat Space Environ Med 1989;60:599-600.
58. Pinelli J, Ferguson MK. Transporting high-risk newborns: The importance of communication. Neonatal Network 1985;June:23-26.
59. Finsterwald W. Neonatal transport: Communication—The essential element. J Perinatol 1988;8:358-360.
60. Chameides L, ed. Textbook of pediatric advanced life support. Dallas American Heart Association and American Academy of Pediatrics, 1988.
61. Kallstrom TJ, Salyer JW. The incidence of accidental extubation in a neonatal intensive care unit (abstract). Respir Care 1989;34:1006.
62. Brown MS. Prevention of accidental extubation in newborns. AJDC 1988;142:1240-1243.
63. Kallstrom TJ, Salyer JW, Baldesare KK, Chatburn RL. A comparison of two different endotracheal-tube taping techniques in the neonate (abstract). Respir Care 1990;35:1121-1122.
64. Moss JE, Purohit DM. Drug-induced paralysis (muscle relaxant) therapy in the mechanically ventilated neonate. J Perinatol 1988;8:321-324.
65. Kronick JB, Kissoon N, Frewen TC. Guidelines for stabilizing the condition of the critically ill child before transfer to a tertiary care facility. Can Med Assoc J 1988;139:213-220.
66. Rosetti VA, Thompson BM, Miller J, Mateer JA, Aprahamian C. Intraosseous infusion: An alternative route of pediatric intravascular access. Ann Emerg Med 1985;14:885-888.
67. Glaeser PW, Losek JD. Intraosseous needles: New and improved. Pediatr Emerg Care 1988;4:135-136.
68. Wagner MB, McCabe JB. A comparison of four techniques to establish intraosseous infusion. Pediatr Emerg Care 1988;4:87-91.
69. Ridenour J, Schreiber V, Kelin K, Heller M, Menegazzi J. Noise exposure to flight crew from the MBB BO-105 and MBB BK-117 (abstract). J Air Med Transport 1990;9:76.
70. Hunt RC, Bryan DM, Brown VS, Whitley TW, Benson NH. Inability to assess breath sounds during air transport in a MBB BO-105 helicopter (abstract). J Air Med Transport 1989;8:47.
71. Campbell AN, Lightsone AD, Smith JM, Kirpalani H, Perlman M. Mechanical vibration and sound levels experienced in neonatal transport. AJDC 1984;138:967-970.
72. Gerard J, MacLeod BA, Heller MB, Yealy DM. Verification of endotracheal intubation using a disposable end-tidal CO_2 detector (abstract). J Air Med Transport 1989;8:48.
73. Higgins D, Hayes M, Denman W, Wilkinson DJ. Effectiveness of using end-tidal carbon dioxide concentration to monitor CPR. Br Med J 1990;300:581-582.
74. Ours J, et al. Evaluation of the effectiveness and usefulness of a disposable end-tidal CO_2 detector in the prehospital/interhospital setting of urban helicopter flight nursing. J Air Med Transport 1990;9:69.
75. Coleman L. Modification in respiratory equipment for neonatal transport: One team's experience. J Air Med Transport 1990;9:10-11.
76. Hankins CT. The use of pulse oximetry during infant transport from outside facilities. J Perinatol 1988;8:346.
77. McGuire TJ, Pointer JE. Evaluation of a pulse oximeter in the prehospital setting. Ann Emerg Med 1988;17:1058-1062.
78. Giard DA, Ross CS. The use of pulse oximetry in prehospital treatment and transport. Denver: Ohmeda Inc, 1989.
79. Adams KS, Branson RD, Hurst JM. Monitoring oxygenation with oximetry during transport. Respir Management 1987;17:63-69.

80. Peterson C, Budd R, Tjelmeland K. Comparative evaluation of three end-tidal carbon dioxide monitors during flight (abstract). J Air Med Transport 1990;9:70.
81. Tjelmeland K, Poser B, Budd R, Peterson C, Bodenstedt R. Evaluation of the accuracy of the end-tidal carbon dioxide monitor during altitude changes using the canine model (abstract). J Air Med Transport 1990;9:71.
82. Ross C, Renzi F. Role of pulse oximetry in the initial airway management of helicopter transported trauma victims (abstract). J Air Med Transport 1990;9:88.
83. Kelleher JF. Pulse oximetry. J Clin Monit 1989;5:37-62.
84. Salyer JW, Lewis DD. Pulse oximetry: Application in the pediatric and neonatal critical care unit. AACN Clin Issues Crit Care Nurs 1990;1:339-347.
85. Pekka T, Nichols RJ, Traber DL. Monitoring patients during helicopter flight. J Clin Monit 1990;6:139-140.
86. Talke P, Nichols RJ, Traber DL. Does systolic blood pressure measured using a pulse oximeter correlate with conventional methods. J Clin Monit 1990;6:5-9.
87. Pascucci RC, Schena JA, Thompson JE. Comparison of a sidestream and mainstream capnometer in infants. Crit Care Med 1989;17:560-562.
88. Salyer JW, Rogers M, Myer T, Chatburn RL. An evaluation of the accuracy of the Ohmeda Oxicap 4700 in a neonatal population (abstract). Respir Care 1990;35:1128-1129.
89. Chatburn RL, Salyer JW. Physiologic monitoring. In: Chatburn RL, Lough MD, eds. Handbook of respiratory care. 2nd ed. Chicago: Mosby-Year Book, 1990:59-122.

Salyer Discussion

Barnes: I would like to comment on the heat-moisture exchangers that you suggested. The most efficient puts out 29 mg/L and the worst only 14 mg/L, with the endotracheal tube adding 5 to 8 mg/L.[1,2] For a few hours they are fine, but if you have a 3- or 5-hour transport, I would suggest that you may have problems with thick secretions.

1. ECRI. Heat and moisture exchangers. Health Devices 1983;12:155-167.
2. Mebius C. A comparative evaluation of disposable humidifiers. Acta Anaesthesiol Scand 1983; 27:403-409.

Salyer: I agree, I think they need a lot more study before we consider using them in the neonate.

Hess: A couple of things, John (Salyer). First of all, I was pleased to see you address the electromagnetic interference (EMI) issue. The way to get around the EMI problem is by shielding your equipment. If the equipment is properly shielded, then the equipment doesn't produce any EMI. But I think just as importantly with some of the newer equipment that is microprocessor-based, is that the equipment also doesn't receive EMI. There are some cases, at least anecdotal, of EMI interference shutting down microprocessor ventilators. So, I think for those of us who are respiratory care practitioners, EMI is a concern—not only for it going out but also for it coming into equipment. I really appreciate your comments on that. The second point that I wanted to make has to do with the Fenem device (the end-tidal CO_2 device). As you pointed out in your slide, I think one of the problems with those devices is that they do have a pretty high false-positive rate for esophageal intubation if the patient is in cardiac arrest. In other words, as you pointed out on the slide, if the patient is in cardiac arrest, the tube can be in the trachea but the Fenem doesn't change color—leading the practitioner to believe that it's in the esophagus because CO_2 is not being delivered to the lungs so that it can be exhaled. These devices, I believe, are used primarily in adults. Are you concerned as a pediatric respiratory care practitioner that these devices do add some dead space to the airway? Also, they seem to be pretty heavy to put on a neonatal or pediatric endotracheal tube. Are you concerned about them causing misplacement of the airway?

Salyer: We are concerned. Those are good points, Dean! The effect of adding dead space to the airway in continuous flow infant ventilators is an issue that has always confused me. I've heard great concerns expressed about adding dead space to neonatal airways by putting on larger adapters, but, I'm not sure how important that is in a continuous-flow system. I've put dead space on purpose on infants who had very low P_{CO_2}s, but couldn't tolerate extubation and were on very low frequencies. I put 60 mL between the Y of the ventilator tubing and the patient's endotracheal tube. I found no important change in the P_{CO_2}, and I think we just washed the gas out of the dead space by the continuous flow of the ventilator circuit, but I am still concerned. More important is the issue of weight. With any adapter you put in line, especially in transport, you've got to be very careful about contributing to accidental extubations.

O'Rourke: While I agree with the importance of having a safe transport of a baby into the hospital, at a recent critical-care symposium the issue came up about the morbidity and mortality of in-hospital transport, ie, to the CAT scanner, to x-ray, to OR. This is another area that unfortunately gets ignored. The number of

vital-sign changes that occur with just moving the child across the hall (let alone in and out of a vibrating helicopter) are immense.

Salyer: I completely agree! I just did not have time to address all of the issues here, but the intrahospital transport of patients is a big issue, and we have had a number of situations in which patients have deteriorated when we were transporting them for diagnostic procedures within the hospital. This subject is treated in Mark Rogers' text, *Pediatric Intensive Care*.[1]

1. Rogers M. Pediatric intensive care. Baltimore: Williams & Wilkins, 1987:1399-1400.

Carlo: You didn't mention ventilators during transport. I wonder, with the marked variability that occurs in pressure, t_i, t_e, and rate with hand bagging, if ventilators should be considered standard practice for transported patients.

Salyer: I certainly do think they should. Also, the issue of which brand or type of transport ventilator (there are many kinds available) is important. I'll agree that there are good devices out there that are not very expensive, and I can't think of good reasons why we shouldn't have one in use for all transports, as opposed to hand bagging.

Chatburn: Just to comment on that issue, there was an abstract[1] presented in New Orleans at the 1990 AARC convention, that showed that the use of an inexpensive airway-pressure manometer that had alarms on it for rate and pressure would alleviate some of the problems that you mentioned. In terms of hand-bagging, that might be less expensive and perhaps a faster and easier alternative to setting up a mechanical ventilator for short-term transports, but, still try to avoid the situation in which you have severe barotrauma when the patient just comes into the nursery right from a transport.

1. MacDonald K, Vinson DL, Salaz E, Webb D. Evaluation of the Sechrist BreathTracker Manometer (abstract). Respir Care 1990; 35:1125.

Mathews: My first question regards pulse oximetry. Have you tried using the new reflectance type of sensors?

Salyer: I have no experience with them.

Mathews: We ran a study, which we're writing a paper on now, where we sequentially monitored 286 normal, healthy people. First we used a transmissive sensor and immediately followed with a reflectance-type sensor, and in the initial data analysis found apparently no difference. The benefit of this type of sensor is that you can put it in central location (you can put it on a flat surface). And therefore you can move from forehead to chest wall, perhaps even on the back, which is generally pretty stable. This may take care of some of the motion artifact and more 'centralize' the circulation that you're measuring. So, it's something you might want to look at.

Secondly, getting back to the RCP and the team, I want to ask you what skills you think the RCP brings to the team that makes him a valuable member of that team.

Salyer: That's a good question! And, I'll answer it by saying that in the papers in which they do not report a RCP as a team member, they generally send an anesthesia resident. I would say that RCPs can be valuable members of the team if they are rigorously trained, and are experienced in airway management, respiratory assessment and ventilator support. Those are the three areas that I think are important.

Mathews: As you know, there's a lot of controversy within the flight-therapy groups as to whether it should be mandatory that therapists also be EMTs or a paramedics. What are your feelings on that?

Salyer: I guess I haven't given that very much thought, Paul. I could shoot from the hip, but it wouldn't be a very informed opinion. So, I'll refrain from answering that.

O'Rourke: I think one thing that has to be looked at is the shortage of (1) RTs and (2) nurses. We can't staff our units, let alone staff a 24-hour/day, 7-day/week transport system. And, I personally think that the only transport systems that work are those that have consistent services every day of the week. I think we need to look at the problems we have in our hospitals, and given the shortages, I would rather have that expertise in the hospital.

Salyer: Do you find there are times when you want a therapist and they cannot provide you one because there are not enough people?

O'Rourke: Oh yes. We have come to the point where we almost had to limit in-hospital ventilators.

Barnes: Hartford Hospital in Connecticut had a similar staffing problem. I think you have to have a really dedicated group of registered therapists who want to serve on the flight team. The Hartford group made it successful by volunteering to be on standby on their own initiative. So, I think you need a core of dedicated RRTs. Hartford Hospital now staffs two helicopter crews, but, when they first started, they had the same problem. So, I think you start with a high level of commitment on the therapists' part and go from there.

Salyer: I agree with that, although I think that Dr O'Rourke is right—we have a serious manpower shortage. The debate at the 1990 AARC convention in New Orleans about 1- or 2-year graduates was punctuated by remarks that we don't have enough people to do the work we are doing now, and if we start eliminating 1-year schools, we're going to have even fewer RCPs. It's a serious problem and it's not going to go away.

Bronchial Hyperreactivity in Infants

Thomas A Hazinski MD

Introduction

In this review, I focus on the clinical disorder of bronchial hyperreactivity (BHR) in infants—what it is, its pathophysiologic mechanisms, how it is measured, and clinical disorders that are associated with or mimic BHR. I also discuss the therapeutic implications of acute and chronic bronchial hyperreactivity and identify opportunities for research.

BHR is defined as expiratory airflow limitation that can be provoked by agents that directly or indirectly cause airway smooth-muscle constriction. BHR can also be defined as expiratory airflow limitation that is present at baseline and improves in response to agents that relax airway smooth muscle. It is important to note that bronchoconstrictor tone is present in the airway smooth muscle of normal individuals; beta-agonist inhalation increases expiratory airflow even in patients without demonstrable airway disease.[1] Also, it is possible to provoke bronchoconstriction in subjects with normal lungs by using large or prolonged exposure to constrictor agents; however, BHR is said to be present when airflow limitation is produced by low doses of constrictor agents.

Agents that provoke expiratory airflow limitation are shown in Table 1. These agents are divided into those that directly stimulate airway smooth muscle (cholinergic stimulation, histamine, methacholine, and perhaps cold air)[2] and those that indirectly reduce expiratory airflow by interacting with other cells in the lung that release substances that reduce airway caliber. Alveolar and interstitial macrophages, eosinophils, platelets, and endothelial cells have all been shown to release peptides, lipids, and metabolites of arachidonic acid and other mediators that constrict smooth muscle, cause airway edema, and increase airway mucus production. The reader is directed to several recent references for review of the role of these mediators.[3-9]

Table 1. Promoters of Bronchoconstriction

Direct
Acetylcholine and substance P (released by parasympathetic nerves)
Histamine or methacholine
Cold air
Indirect
Exercise
Sulfur dioxide (SO_2)
Allergens
Tobacco smoke
Infection-inflammation substances (released by granulocytes, macrophages, eosinophils, or endothelial cells)

Detection of Bronchial Hyperreactivity

The hallmark of BHR is demonstration of the provocation or presence of reversible expiratory airflow limitation. In cooperative older children and adults, measurements of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and quantitative expiratory flow-volume

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Abbreviations Used in This Paper

BHR	— Bronchial hyperreactivity
BPD	— Bronchopulmonary dysplasia
FEV_1	— Forced expiratory volume in 1 second
FRC	— Functional residual capacity
FVC	— Forced vital capacity
MEF_{25}	— Maximal expiratory flow at 25% of vital capacity
PEFV	— Partial expiratory flow volume
RSV	— Respiratory syncytial virus
VIP	— Vasoactive intestinal peptide
$\dot{V}_{maxFRC}$	— Maximum expiratory flow at FRC

curves—before and after the inhalation of bronchodilators—have been used to assess BHR.[10] With these measurements, the time course and magnitude of the bronchoconstrictor response to any provocative agent can be defined. Protocols have been standardized to relate a specific degree of airflow limitation, such as a 20% fall in FEV_1, to a specific dose of inhaled bronchoconstrictor. BHR is said to be present when airflow limitation can be induced by a low concentration of a cholinergic agent or when a usually innocuous agent, such as cold air or mild exercise, results in a fall in expiratory flow.

Regardless of the provocative agent used, the time course of the bronchoconstrictor response is similar in patients with BHR. That is, within several minutes of the administration of the provocative agent, flowrates are reduced, and within 30-60 minutes of administration (or more rapidly if a bronchodilator is administered) flowrates return to baseline. This acute decrease in expiratory airflow may be associated with wheezing, prolonged expiratory time, and abnormal gas exchange, but these clinical signs are difficult to quantify and are rarely measured.

In addition to the acute reduction in airflow, some individuals with BHR demonstrate recurrent airway obstruction 3-8 hours after provocation by allergen inhalation or exercise.[11] This 'late-phase' response is also thought to be related to the release of cell-derived bronchoconstrictor substances and to airway wall edema, mucus production, and peribronchiolar inflammation. Although common in children with asthma, the late-phase response has not been systematically examined in infants. However, there is reason to believe that this late-phase response, if left untreated, may be linked to the development of chronic bronchial hyperreactivity or asthma.[11]

Bronchial Hyperreactivity in Infants

Based on old anatomic data,[12] several generations of physicians and respiratory care practitioners have been taught that young infants have little capacity to respond to bronchoconstrictor stimuli. Until recently, it has been impossible to objectively measure BHR in infants because maximum inspiratory and expiratory flows could not be reliably measured in these uncooperative subjects. However, in the past 5 years two techniques have been developed to objectively measure BHR in infants. In one technique, a partial expiratory flow-volume (PEFV) curve is generated during a normal exhalation followed by a forced exhalation. First described by Adler and Wohl,[13] and developed further by Godfrey et al[14] and Tepper et al,[15] the forced exhalation is generated by a squeeze or hug technique in which a preset amount of positive pressure is rapidly applied to the sedated infant's chest at the end of a tidal inspiration. Expiratory airflow is measured via a pneumotachograph attached to the endotracheal tube or face mask. The two curves are superimposed, and the flowrate of the squeezed breath is measured at the end-expiratory point on the volume axis of the tidal breath. The pressure applied to the chest is increased until the maximal flowrate is achieved. This value has been termed the $\dot{V}_{maxFRC}$ and is shown graphically in Figure 1. Other investigators have quantitated different parts of the curves to yield other variables.[16]

A second technique used to measure BHR in infants has been described by Motoyama.[17] This technique is similar to the traditional maximum expiratory flow-volume maneuver. By either manual lung inflation or CO_2 inhalation, a large inspiration is generated in the infant, and then the airway is rapidly deflated by connecting the infant's airway to a reservoir of negative pressure. This technique has been used most often in intubated and sedated patients.

Methodologic aspects of these techniques were reviewed by Turner et al in 1990.[18] The two major

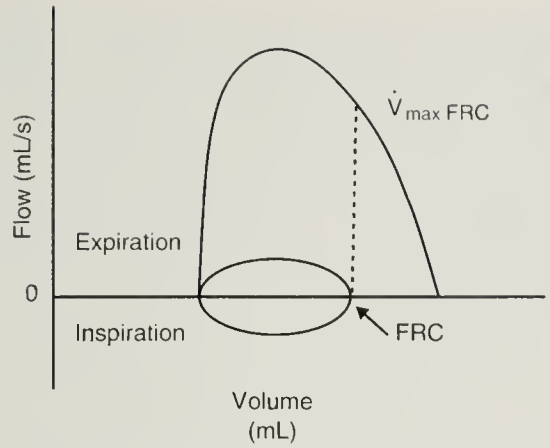

Fig. 1. Partial expiratory flow-volume (PEFV) curve. Smaller inner curve—tidal breathing; larger curve—forced expiratory maneuver. Maximal expiratory flow at functional residual capacity ($\dot{V}_{maxFRC}$, mL/s) is indicated by dashed line; and difference between tidal breathing and maximal expiratory flow represents expiratory flow reserve. (Reprinted, with permission, from Reference 15).

limitations of interpreting data derived from these methods are (1) that the actual delivered dose of provocative agent (ie, either bronchodilator or bronchconstrictor) is difficult to quantify and (2) that the sites of airflow limitation and improvement cannot be precisely identified. For example, some experts believe that upper-airway caliber may be reduced by bronchoconstrictor challenge. Therefore, data derived from intubated patients may not be comparable to data derived from infants breathing via a face mask.

Despite these limitations, the techniques have been applied in infants to serially assess airflow before and after the administration of traditional bronchoconstrictor agents. In many of these studies, the concentration of inhaled agents that produces a predetermined fall in flow (usually 20-40% fall in $\dot{V}_{maxFRC}$) is computed. Recently it has been reported that normal infants (less than 24 months of age) exhibit reduced $\dot{V}_{maxFRC}$ after inhaling relatively low concentrations of methacholine, histamine,[19-23] or cold air.[24] A typical methacholine challenge test is shown in Figure 2. Using this technique, it has been found that infants develop bronchoconstriction at lower concentrations of cholinergic stimuli than do children and adults.[19] Some have interpreted these data to indicate that infant airways are more reactive than adult airways.[22] Others assert that current methods of aerosol administration during provocative studies are simply more efficient in infants than in older individuals because older individuals entrain room air during the inhalation of provocative agents whereas infants may not. Therefore, the apparent hypersensitivity of infant airways to bronchoconstrictor agents may be an artifact of the drug delivery system. In a recent study, LeSouëf and his coworkers[20] have corrected data from previously published studies to account for the problem of air entrainment and have concluded that airway reactivity is similar in infants, children, and adults.[21] This controversy has not yet been settled, and it highlights the lack of data regarding drug deposition in infant airways and the need for future research.

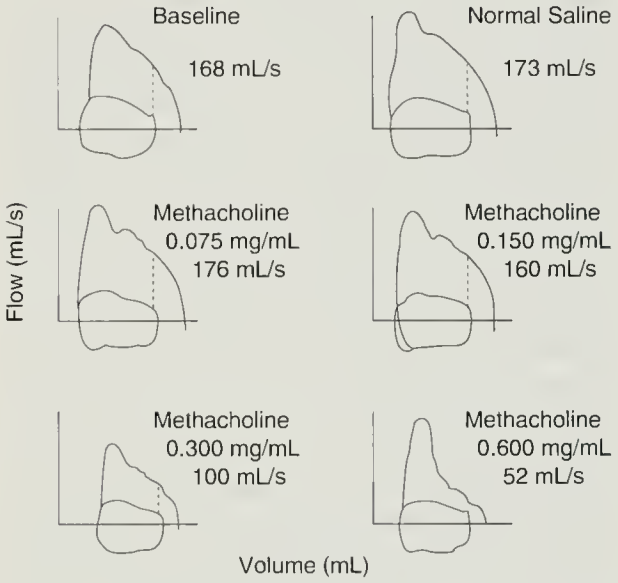

Fig. 2. Partial expiratory flow-volume (PEFV) curves during the methacholine bronchial challenge test. There is no significant change in either maximal expiratory flow at functional residual capacity ($\dot{V}_{maxFRC}$,) or shape of the PEFV curve between base line and after inhalation of normal saline or the two lowest concentrations of methacholine (0.075, 0.150 mg/mL). However, following next 2 higher concentrations (0.300 and 0.600 mg/mL), there is a progressive decrease in $\dot{V}_{maxFRC}$, and development of a concave shape to the PEFV curve. (Reprinted, with permission, from Reference 23).

Bronchial hyperreactivity is also demonstrable in extremely premature infants during the first weeks

of life. Using cold air as a stimulus for bronchoconstriction, Motoyama et al[25] have shown that even infants born at 26 weeks gestation can develop clinically important bronchoconstriction. In these infants, airflow limitation induced by cold air could be rapidly reversed with beta-agonist inhalation—indicating that this stimulus did not damage the airways or cause clinically important edema, and suggesting that increased bronchial smooth-muscle tone was responsible for some of the provoked airflow limitation.

Etiology of Chronic Bronchial Hyperreactivity in Infants

Although sensitive provocative techniques may reveal hyperreactivity in normal infants, the vast majority of infants do not exhibit signs of acute or chronic airway hyperreactivity. Why is it then that some infants develop acute or chronic wheezing that requires therapy? Some investigators feel it is merely a consequence of the small airway caliber and unique geometry that is present in the rapidly growing lung. Although this factor undoubtedly plays a role, three other causes of chronic bronchial hyperreactivity have been suggested. First, it is possible that some infants are genetically determined to develop BHR or asthma. Evidence to support this proposition comes from studies of asthma incidence in Australian twins[26] and from studies by Taussig et al.[27] A second possibility is that chronic BHR is a consequence of early episodes of acute lung injury such as bronchiolitis, ARDS, and inhaled environmental pollutants such as tobacco smoke and sulphur dioxide.[28,29] Of course, it is possible that respiratory infections were simply more severe in those infants with a genetically determined tendency for BHR.

A third possible cause of BHR is premature birth.[30] A small but elegant study by Bernard et al[29] clearly showed that premature birth, even when unaccompanied by respiratory failure and its treatment, resulted in detectable abnormalities in small airway function in the second decade of life. This study, which employed three control groups (healthy unrelated children, term siblings of premature infants with respiratory failure, and term siblings of premature infants without respiratory failure) also showed that the mothers of infants born prematurely had a higher incidence of BHR than did mothers of term infants—suggesting a link between maternal BHR and premature labor. It is likely that chronic bronchial hyperreactivity is multifactorial and influenced by both genetic and environmental factors. It is unlikely that even large-scale epidemiologic studies will be powerful enough to unravel these interacting influences.

Clinical Conditions that Are Associated with Bronchial Hyperreactivity

Some of the clinical conditions that are associated with airway hyperreactivity in infants are listed in Table 2.

Table 2. Clinical Conditions Associated with Bronchial Hyperreactivity

Bronchopulmonary dysplasia
Aspiration
Gastroesophageal reflux
Pulmonary edema and congestive heart failure
Viral bronchiolitis
Cystic fibrosis
Asthma
Lung transplantation

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) has become the most common chronic obstructive lung disease of infancy. Infants with BPD exhibit abnormal lung mechanics, signs of chronic respiratory distress, and abnormal chest radiographs, and may require long-term mechanical ventilation and/or oxygen therapy. The lung pathology of BPD is focal and complex and includes airway metaplasia, interstitial fibrosis, and, as demonstrated in some autopsy studies, peribronchial smooth-muscle hypertrophy and hyperplasia.[31] BPD is known to cluster in atopic families,[32] leading some investigators to conclude that the development of severe BPD has a strong genetic component. Motoyama et al[25] have shown that infants with BPD have increased bronchoconstrictor tone that can be rapidly reversed by

inhaled beta-agonists. However, the relevance of these observations in terms of therapy is not known because no studies exist of long-term treatment with bronchodilator-like drugs. Moreover, it may be that in these infants, airway inflammation and airway-wall instability may play more important roles in the determination of airway caliber than does BHR. Indeed, recent histologic studies of BPD by Stocker[33] demonstrate the remarkable variety of airway and parenchymal abnormalities in BPD infants. In addition, the ventilation-perfusion abnormalities manifested by these patients include a poorly defined pulmonary vascular hyperreactivity that may actually be worsened by vasodilator therapy.

Respiratory-Syncytial-Virus Bronchiolitis

Although the controversy is now decades old, current evidence indicates that the majority of infants with bronchiolitis caused by the respiratory syncytial virus (RSV) have bronchial hyperreactivity with a clinical course that can be improved by bronchodilator therapy.[34] In this condition, the precise cause of BHR is not clear. It is possible that RSV infection unmasks a genetically determined predisposition for BHR. Alternatively, perhaps multiple environmental factors are required for severe RSV infections to become symptomatic. For example, Groothius et al[35] observed that infants with severe RSV bronchiolitis were more likely to live in crowded households and in households where passive exposure to tobacco smoke occurs.

Pulmonary Edema and Congestive Heart Failure

Pulmonary edema resulting from either cardiac failure or increased lung capillary permeability can cause wheezing and tachypnea. It has long been known that in patients with pulmonary edema the administration of drugs with diuretic properties can improve lung function and gas exchange even before a brisk diuresis has occurred. The traditional explanation for this observation has been that diuretic therapy reduces interstitial lung edema and reduces the peribronchial puddling of edema fluid that may affect airway caliber. However, recent studies in adults demonstrate that BHR is present in patients with pulmonary edema and can be reversed rapidly by beta-agonist administration.[36] The mechanism by which congestive heart failure induces BHR is unknown, but may be related to the effect of edema on bronchial vascular tone, ion transport, extracellular ion concentration, or airway osmolality. Moreover, the results of recent studies using the inhaled diuretic amiloride,[37] inhaled furosemide,[38] and low-dose orally administered furosemide (in pediatric patients with BPD)[39] suggest that modulation of epithelial ion transport may be an important factor in determining airway tone.

Lung Transplantation

Single and double lung transplantation has become a feasible treatment for persons with end-stage pulmonary disease. Surprisingly, perhaps, BHR has been observed in adult patients who have received lung and heart-lung transplants.[40] Although BHR has not yet been described in infant transplant recipients, this finding in adults is noteworthy for several reasons. Because transplanted lungs are either totally or partially denervated, the observation of BHR in these lungs indicates that central cholinergic innervation is not necessary for maintaining bronchoconstrictor tone and that other factors, such as mucociliary clearance, epithelial ion transports, or abnormal mucus production, may be involved. Also, these adult transplant recipients had BHR despite high-dose corticosteroid therapy and in the absence of tissue rejection, indicating that the disorder may be very difficult to treat in some patients.

Bronchial Asthma

The most common form of chronic BHR is bronchial asthma, a multifactorial disorder of complex etiology. Asthma has been functionally defined as airflow limitation that varies with time, is reversible, and is hyperresponsive to external stimuli, which may be specific (eg, allergen exposure) or nonspecific (eg, histamine).[41,42] Despite major advances in the understanding of asthma, its pathogenesis remains largely a mystery. The recent

finding that the lungs of asthmatic patients lack the bronchodilator vasoactive-intestinal-peptide (VIP) in cholinergic nerve endings[43] suggests that asthma may result from an imbalance between neurotransmitters that cause bronchodilation and those that cause bronchoconstriction.

Despite the widespread belief that chronic asthma begins in infancy and that chronic airway inflammation is associated with persistent or recurrent bronchoconstriction, there has been a reluctance to diagnose asthma in infants with recurrent episodes of cough, wheezing, and atelectasis. Such infants are still commonly treated with multiple courses of antibiotics and antitussive drugs. Morbidity and mortality rates for asthma continue to increase,[44,45] and childhood asthma remains a costly and emotionally difficult chronic disease. The role of inflammation in airway narrowing has been demonstrated,[46] and there is a growing consensus that beta-adrenergic agents and methylxanthines alone may be insufficient therapy for chronic BHR because they do not affect airway inflammation or edema formation. However, it is heartening to note that the federal government has announced the organization of a multicenter trial of long-term anti-inflammatory agents (eg, cromolyn and corticosteroids) for the treatment of childhood asthma.

Conditions that Mimic Bronchial Hyperreactivity

Even though respiratory care practitioners are commonly taught that all that wheezes is not asthma and that many patients with asthma may not wheeze, these aphorisms are frequently forgotten in the management of individual infants with respiratory distress. Several disorders can mimic BHR in infants (ie, cause wheezing and respiratory distress) but not respond to bronchodilator therapy (Table 3). Perhaps the most common of these abnormalities is tracheomalacia, a congenital disorder in which the airways lack sufficient rigidity. In tracheomalacia, there is deformation and collapse of the airway during the expiratory phase of the respiratory cycle when pleural pressure exceeds intra-airway pressure. Infants with tracheomalacia may exhibit wheezing that is refractory to beta-agonist therapy. Panitch et al[47] have used the squeeze technique to investigate the determinants of expiratory airflow in infants with tracheomalacia. Figure 3 depicts their paradoxical results, which indicate that airflow limitation worsened with beta-agonist treatment and improved with methacholine administration. These data nicely demonstrate the important role that airway smooth-muscle tone plays in the maintenance of airway stability in the infant lung with maturational delay of airway development. These data also may explain why some wheezy infants do not improve with beta-agonist therapy. Similar findings have also been demonstrated in children with cystic fibrosis[48,49] and in some infants who may require large-airway bronchoconstriction to maintain airway stability in the presence of chronically injured airways.[50]

Table 3. Conditions that Mimic Bronchial Hyperreactivity by Causing Large-Airway Instability

Tracheomalacia
Cystic fibrosis
Bronchopulmonary dysplasia
Vascular rings
Tracheoesophageal malformations
Obstructing airway lesions (eg, polyps, hemangiomas)

The diagnosis of asthma in infants should be made only after other disorders that mimic or are associated with BHR are thoroughly considered. The respiratory care practitioner should resist jumping to the conclusion that asthma is present, and should maintain a healthy skepticism concerning diagnosis until appropriate history, physical examination, and laboratory tests exclude other causes of wheezing (listed in Table 3).

Chronic BHR in Infants: Research Opportunities

Despite many advances, substantial gaps remain in our knowledge of the pathogenesis, natural history, and proper treatment of BHR in infants. Advances in at least six areas are desperately needed: (1) There must be renewed emphasis on early di-

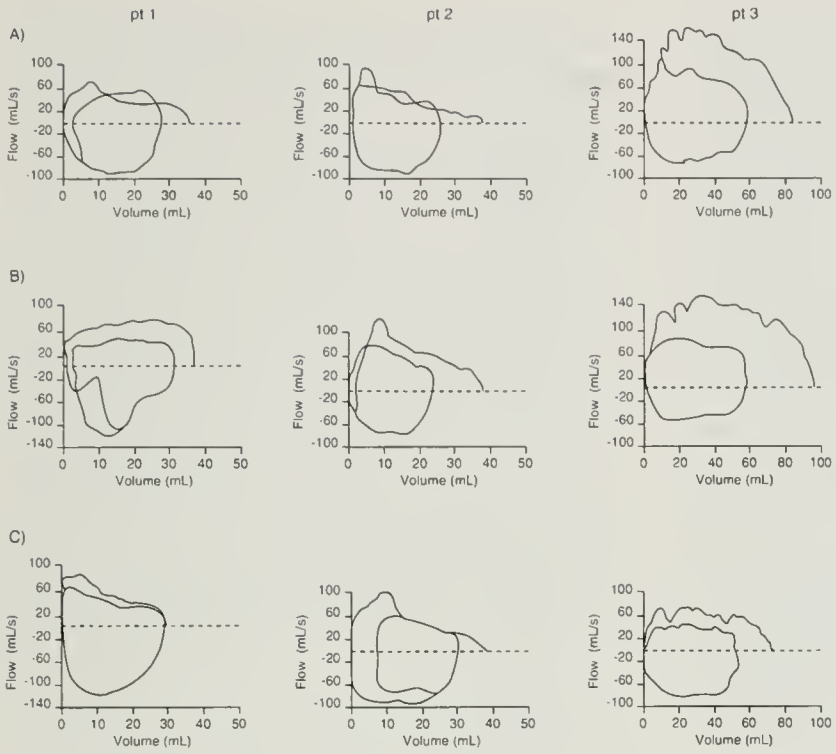

Fig. 3. Best partial expiratory flow-volume (PEFV) curves (obtained with the squeeze technique) for three infants with tracheomalacia at baseline (A), after methacholine (B), and after albuterol (C). Each curve includes both tidal flow-volume (small loop) and forced expiratory flow-volume curves. (Reprinted, with permission, from Reference 47).

agnosis of infants with symptomatic BHR, especially in high risk groups, so that proper therapy (including treatment with cromolyn-like drugs and corticosteroids) and environmental control measures can be initiated as early as possible. The adverse effects of passive smoking on wheezy infants have been unequivocally established;[51,52] therefore, tobacco smoking should be eliminated in areas where such infants are cared for. (2) Safe and effective inhaled corticosteroid preparations such as budesonide[53] should be made available in the U.S., because other steroid preparations either cannot be delivered effectively via nebulization or are absorbed through the lung to cause side effects similar to those of oral steroids.[54] (3) Practicing physicians who treat infants must embrace the concept of chronic anti-inflammatory therapy (ie, cromolyn or corticosteroids) as part of the treatment for moderate asthma. (4) More accurate methods for delivering aerosolized drugs to infants need to be developed and validated.[55] (5) Longitudinal studies of BHR in cohorts of affected infants should be performed to identify the natural variability of BHR. (6) The potential therapeutic role for agents such as furosemide and cromakalim that affect ion transport across airway epithelium should be investigated.[56]

The respiratory care practitioner can play an important role by educating physicians and other care providers about these issues and by not relying on old dogma but instead considering each patient individually. For example, it is inappropriate to withhold a trial of bronchodilator therapy from an infant with RSV bronchiolitis just because one believes that such infants don't respond to bronchodilators. A better approach would be to carefully note respiratory rate and effort, oxygen saturation, level of activity, and lung sounds before and after a therapeutic trial of bronchodilators.

Summary

Intrinsic bronchial hyperreactivity is common in infants and may in part explain why infants develop respiratory distress and wheezing more frequently than do children or adults. Although bronchoconstriction tone is present in infants with normal lungs, some infants seem to be unusually

susceptible to pharmacologic and naturally occurring triggers of bronchoconstriction. Techniques that produce expiratory flow-volume curves by applying positive pressure to the infant's chest or by applying negative pressure to the infant's airway can quantitate BHR in infants. Although methodologic uncertainties exist, these techniques should prove useful in the clinical evaluation of possible treatment strategies for BHR. Despite the fact that many conditions can cause or mimic BHR, bronchial asthma remains the most important disorder associated with BHR. Because of the important role that inflammation plays in asthma and the ineffectiveness of beta-agonist therapy in controlling inflammation, attention in asthma managment has shifted to the possible long-term benefits of inhaled anti-inflammatory agents (eg, cromolyn-like drugs and corticosteroids). The respiratory care practitioner can play a key role in the design, conduct, interpretation, and implementation of studies focusing on the pathogenesis, natural history, and management of bronchial hyperreactivity in infants.

REFERENCES

1. Josephs LK, Gregg I, Mulee MA, Holgate ST. Nonspecific bronchial reactivity and its relationship to the clinical expression of asthma. Am Rev Respir Dis 1989;140:350-357.
2. Goyal RK. Muscarinic receptor subtypes. N Engl J Med 1989;321:1022-1029.
3. Beasley R, Roche WR, Roberts JA, Holgate ST. Cellular events in the bronchi in mild asthma and after bronchial provocation. Am Rev Respir Dis 1989; 139:806-817.
4. LaGente V, Chabrier PE, Mencia-Huerta JM, Braquet P. Pharmacological modulation of the bronchopulmonary action of the vasoactive peptide, endothelin, administered by aerosol in the guinea-pig. Biochem Biophys Res Commun 1989;158:625-632.
5. Metzer WJ, Sjoerdsma K, Richerson HB, et al. Platelets in bronchoalveolar lavage from asthmatic patients and allergic rabbits with allergen-induced late phase responses. Agents Actions Suppl 1987;21:151-159.
6. Nsouli TM, Nsouli SM, Bellanti JA. Neuroimmunoallergic inflammation: New pathogenetic concepts and future perspectives of immediate and late allergic reactions. Part II. Ann Allergy 1988;60:483-494.
7. Rankin JA. The contribution of alveolar macrophages to hyperreactive airway disease. J Allergy Clin Immunol 1989;83:722-729.
8. Wardlaw AJ, Dunnette S, Gleich GJ, Collins JV, Kay AB. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma: Relationship to bronchial hyperreactivity. Am Rev Respir Dis 1988;137:62-69.
9. Wilson MC, Irvin CG, Larsen GL. Inflammation and asthma. Semin Respir Med 1987;8:279-286.
10. Irvin CG. Airways challenge. Respir Care 1989;34:455-463.
11. Barnes PJ. New concepts in the pathogenesis of bronchial hyperresponsiveness and asthma. J Allergy Clin Immunol 1989;83:1013-1026.
12. Engel S. Lung structure. Springfield IL: Charles C Thomas, 1962:26.
13. Adler SM, Wohl MEB. Flow-volume relationships at low lung volume in healthy term newborn infants. Pediatrics 1978;61:636-640.
14. Godfrey S, Bar-Yishay E, Arad I, Landau LI, Taussig LM. Flow-volume curves in infants with lung disease. Pediatrics 1983;72:517-522.
15. Tepper RS, Morgan WJ, Cota K, Wright A, Taussig LM. Physiologic growth and development of the lung during the first year of life. Am Rev Respir Dis 1986;134:513-519.
16. LeSouëf PN, Hughes DM, Landau LI. Shape of forced expiratory flow-volume curves in infants. Am Rev Respir Dis 1988;138:590-597.
17. Motoyama EK. Pulmonary mechanics during early postnatal years. Pediatr Res 1977;11:220-223.
18. Turner DJ, Morgan SEG, Landau LI, LeSouëf PN. Methodological aspects of flow-volume studies in infants. Pediatr Pulmonol 1990;8:289-293.
19. Montgomery GL, Tepper RS. Changes in airway reactivity with age in normal infants and young children. Am Rev Respir Dis 1990;142:1372-1376.
20. Collis GG, Cole CH, LeSouëf PN. Dilution of nebulized aerosols by air entrainment in children. Lancet 1990;336:341-343.
21. Stick SM, Turnbull S, Chua HL, Landau LI, LeSouëf PN. Bronchial responsiveness to histamine in infants and older children. Am Rev Respir Dis 1990;142:1143-1146.
22. LeSouëf PN, Geelhoed GC, Turner DJ, Morgan SEG, Landau LI. Response of normal infants to inhaled histamine. Am Rev Respir Dis 1989;139:62-66.
23. Tepper RS. Airway reactivity in infants: A positive response to methacholine and metaproterenol. J Appl Physiol 1987;62:1155-1159.
24. Geller DE, Morgan WJ, Cota KA, Wright AL, Taussig LM. Airway responsiveness to cold, dry air in normal infants. Pediatr Pulmonol 1988;4:90-97.
25. Motoyama EK, Fort MD, Klesh KW, Mutich RL, Guthrie RD. Early onset of airway reactivity in premature infants with bronchopulmonary dysplasia. Am Rev Respir Dis 1987;136:50-57.
26. Duffy DL, Martin NG, Battistutta D, Hopper JL, Mathews JD. Genetics of asthma and hay fever in Australian twins. Am Rev Respir Dis 1990;142:1351-1358.

27. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig L. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N Engl J Med 1988;319:1112-1117.
28. Weiss ST, Tager IB, Munoz A, Speizer FE. The relationship of respiratory infections in early childhood to the occurrence of increased levels of bronchial responsiveness and atopy. Am Rev Respir Dis 1985; 131:573-578.
29. Bertrand JM, Riley SP, Popkin J, Coates AL. The long-term pulmonary sequelae of prematurity: The role of familial airway hyperreactivity and the respiratory distress syndrome. N Engl J Med 1985;312:742-745.
30. Chan KN, Wong YC, Silverman M. Relationship between infant lung mechanics and childhood lung function in children of very low birthweight. Pediatr Pulmonol 1990;8:74-81.
31. Hazinski TA. Bronchopulmonary dysplasia. In: Chernick V, ed. Kendig's disorder of the respiratory tract in children. Philadelphia: WB Saunders Co, 1990:300-320.
32. Nickerson BG, Taussig LM. Family history of asthma in infants with bronchopulmonary dysplasia. Pediatrics 1980;65:1140-1144.
33. Stocker JT. Pathology of acute bronchopulmonary dysplasia. In: Bancalari E, Stocker JT, eds. Bronchopulmonary dysplasia. New York: Hemisphere Publishing Corp, 1988:237-278.
34. Mallory GB, Motoyama EK, Koumbourlis AC, Mutich RL, Nakayama DK. Bronchial reactivity in infants in acute respiratory failure with viral bronchiolitis. Pediatr Pulmonol 1989;6:253-259.
35. Groothius JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 1988;82:199-203.
36. Cabanes LR, Weber SN, Matran R, et al. Bronchial hyperresponsiveness to methacholine in patients with impaired left ventricular function. N Engl J Med 1989;320:1317-1322.
37. Knowles MR, Church NL, Waltner WE, et al. A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. N Engl J Med 1990;322:1189-1194.
38. Bianco S, Pieroni MG,Refini RM, Rottoli L, Sestini P. Protective effect of inhaled furosemide on allergin-induced early and late asthmatic reactions. N Engl J Med 1989;321:1069-1073.
39. Rush MG, Engelhardt B, Parker RA, Hazinski TA. Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dypslasia. J Pediatr 1990:117:112-118.
40. Maurer JR, McLean PA, Cooper JD, Chamberlain DW, Grossman RF, Zamel N. Airway hyperreactivity in patients undergoing lung and heart/lung transplantation. Am Rev Respir Dis 1989;139:1038-1041.
41. Chung KF, Barnes PJ. Respiratory and allergic disease. I. Br Med J 1988;296:29-33.
42. Dantzker DR, Pingleton SK, Pierce JA, et al. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Official statement of the American Thoracic Society. Am Rev Respir Dis 1987;136:225-244.
43. Ollerenshaw S, Jarvis D, Woolcock A, Sullivan C, Scheibner T. Absence of immunoreactive vasoactive intestinal polypeptide in tissue from the lungs of patients with asthma. N Engl J Med 1989;320:1244-1248.
44. Mellis CM. Important changes in the emergency management of acute asthma in children. Med J Australia 1988;148:215-217.
45. Management of asthma in the community. Lancet 1989;22:199-200.
46. James AL, Pare PD, Hogg JC. The mechanics of airway narrowing in asthma. Am Rev Respir Dis 1989; 139:242-246.
47. Panitch HB, Keklikian EN, Motley RA, Wolfson MR, Schildlow DV. Effect of altering smooth muscle tone on maximal expiratory flows in patients with tracheomalacia. Pediatr Pulmonol 1990;9:170-176.
48. Zach MS, Oberwaldner B, Forche G, Polgar G. Bronchodilators increase airway instability in cystic fibrosis. Am Rev Respir Dis 1985;131:537-543.
49. Pattishall EN. Longitudinal response of pulmonary function to bronchodilators in cystic fibrosis. Pediatr Pulmonol 1990;9:80-85.
50. Prendiville A, Green S, Silverman M. Paradoxical response to nebulized salbutamol in wheezy infants, assessed by partial expiratory flow-volume curves. Thorax 1987;42:86-91.
51. Tager IB, Segal MR, Munoz A, et al. The effect of maternal cigarette smoking on the pulmonary function of children and adolescents. Am Rev Respir Dis 1987; 136:1366-170.
52. Young S, LeSouëf PN, Geelhoed GC, et al. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. N Engl J Med 1991;324:1168-1173.
53. Bisgaard H, Munck SL, Nielsen JP, Petersen W, Ohlsson SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. Lancet 1990:336:649-61.
54. Kerrebijn KF. Use of topical corticosteroids in the treatment of childhood asthma. Am Rev Respir Dis 1990; 141 (2 Pt 2):S77-S81.
55. Newhouse MT, Dolovich MB. Control of asthma by aerosols. N Engl J Med 1986:315:870-874.
56. William AJ, Lee TH, Cochrane GM, et al. Attenuation of nocturnal asthma by cromakalim. Lancet 1990; 336:334-336.

Hazinski Discussion

Rau: I was curious, as a follow-up to your concluding points, with the different causes of airway obstruction—particularly from the inflammatory components—what advice could you give us about improving diagnostic criteria for use of bronchodilators versus other agents like cromolyn or even diuretics (in the traditional use of diuretics)? Do you see any lights at the end of the tunnel?

Hazinski: I'm not very hopeful about the problem of the early detection and treatment of bronchial hyperreactivity. I was a pulmonologist for 4 years, ending in 1984, and then I became a pulmonologist again 2 years ago. In that interval, I thought that the use of antibiotics alone to treat chronic wheezing had sort of disappeared, that physicians had learned during their house-officer training (from pulmonologists or allergists or somebody) that recurrent wheezing doesn't respond well to antimicrobial therapy. But, we continue to see patients whose private pediatricians fail to appropriately treat recurrent cough and wheezing. So, I think we all have an educational mission to educate practicing physicians and house staff about the importance of early detection. The NIH has decided to fund a number of centers to look at early anti-inflammatory therapy in infants with chronic bronchial hyperreactivity, using either traditional therapy, inhaled cromolyn, or inhaled steroids. I hope that that this study will support the use of these agents more frequently. Many house officers and pediatricians are reluctant to use bronchodilator therapy even in acute situations where you lose nothing by trying. They will say "everybody knows that there is not enough smooth muscle in infants' airways to bronchoconstrict, and everybody knows that bronchiolitis is an inflammatory disease, and everybody knows that pulmonary edema doesn't cause wheezing." So, I would ask you what your suggestions are in that regard. Because, all we can do is educate physicians one at a time. It's a very troublesome problem. I don't know if Chris (Green) or David (Orenstein) have any comments . . .

Green: I'll add to that—I see a problem in the hospital with physicians and therapists determining what is wheezing and what is not. Some children make strange respiratory sounds that may sound a little like wheezing or may even be wheezing, but these sounds clear after the child coughs. These sounds are from secretions in the airway. Some of these children have respiratory infections and some may not have bronchial hyperreactivity. Proper interpretation requires careful clinical evaluation rather than routine pulmonary function testing on every child. Therefore, we have an educational role in the clinic, on the hospital ward, or in the office.

Martin: My curiosity was aroused by your comment about the two-lung transplant patients. Traditional teaching would have it that vagal cholinergic pathways to airway smooth muscle are the major mechanism of mediating bronchoconstriction. I would imagine that if you had a lung transplant, the vagus would be denervated and there would no longer be an intact cholinergic pathway.

Hazinski: Well, it's not clear. The paper in the *American Review of Respiratory Disease* (these are adults in the Toronto group) talks about these neuroendocrine cells in the lung that may have cholinergic transmitters in their granules.[1]

I think patients with transplants ought to be a very rich source of research regarding the control of breathing and bronchial hyperreactivity.

1. Maurer JR, McLean PA, Cooper JD, Chamberlain DW, Grossman RF, Zamel N, Toronto Lung Transplant Group. Airway hyperreactivity in patients undergoing lung and heart/lung transplantation. Am Rev Respir Dis 1989;139:1038-1041.

Orenstein: Just a couple of points. Tom (Hazinski), I thought that was a very nice overview of a very common problem. A philosophic point is if you're standing up here in front of us questioning the design of this lung, which it seems that you are, and complaining about being stuck with bronchial smooth muscle and seeing only trouble from that, I think that Howie Panitch's work shows some benefit from having smooth muscle in bronchial walls. His work has shown that babies with tracheomalacia may get better with methacholine and worse with bronchodilator.[1] (He has done this in the lab with muscle strips as well as in vivo with babies.) I think this gives us some hint of a protective role that muscle plays. If other things that normally would maintain patency of the airway are not there because of destruction as Lou Landau[2] showed a number of years ago in patients with cystic fibrosis, then it may be the resting tone of the smooth muscle itself that maintains the patency of the airway. So, maybe it is a backup system for keeping those little tubes open. That's my philosophical point. The other thing is about gastroesophageal reflux (GE reflux). As you pointed out, GE reflux may increase bronchial reactivity. Clinically this can be very difficult to diagnose and manage, at least in part because the bronchodilator agents that we use are pretty stupid: They don't differentiate among different smooth muscles—so if you give a beta-agonist or theophylline, you may well relax bronchial smooth muscle, you may also relax lower-esophageal sphincter smooth muscle. So, whereas you may initially make what you

think is the end organ better, you may be making it worse by increasing reflux—a difficult thing to deal with clinically.

1. Panitch HB, Keklikian EN, Motley RA, Wolfson, MR, Schidlow DV. Effect of altering smooth muscle tone on maximal expiratory flows in patients with tracheomalacia. Pediatr Pulmonol 1990;9:170-176.
2. Landau LI, Phelan PD. The variable effect of a bronchodilating agent on pulmonary function in cystic fibrosis. J Pediatr 1973; 82:863-868.

Green: David (Orenstein) or Tom (Hazinski), do you know if the effects of inhaled beta-adrenergic agents on the lower esophageal sphincter have been studied?

Orenstein: No, I don't know.

Hazinski: I don't either.

Salyer: Would you comment on a particularly frustrating topic for me—a lot of bronchodilator therapy ordered on a lot of infants and children who have no visible signs of wheezing whatsoever? The reason I am asking you this is I am told that it has a beneficial effect on mucociliary clearance. Are you familiar with that literature, and is that really true?

Hazinski: I suspect David (Orenstein) and Chris (Green) know more about that. But, let me just comment about the general problem of requiring wheezing before instituting bronchodilator therapy. I just think of wheezing as just one of five or six symptoms of airway obstruction. We have a bronchiolitis outbreak right now back home. If somebody says, "We tried bronchodilator therapy, but it didn't work," and I say, "What do you mean it didn't work." And they say "well, the baby is still wheezing." I ask, "So what else happened?" They say, "Well, the baby fell asleep, his heart rate went from 190 to 125, his respiratory rate went from 75 to 50, and his oxygen saturation stabilized." And I ask "So, does any of that count as beneficial effects of bronchodilator therapy?" And they say "Oh, well, yes I guess so." But I think there are mistakes made in both directions—you know, requiring wheezing before instituting therapy, or requiring the disappearance of wheezing as a criteria of improvement. There is very little relationship between lung mechanics, lung sounds, and gas exchange—the first two are surprisingly insensitive measurements. In recent reports of transbronchial biopsies on moderately severe, stable asthmatics, and in patients dying with asthma, the transbronchial biopsies in both groups of patients look very similar—there's inflammation all over the place.[1] So I think we have to really rethink this whole business about what asthma really is.

1. Foresi A, Bertorelli G, Pesci A, et al. Inflammatory markers in bronchoalveolar lavage and in bronchial biopsy in asthma during remission. Chest 1990;98:528-535.

Green: To address your (Salyer's) question, to my knowledge terbutaline has been studied, I believe by Sackner's group in Miami, and has been shown to increase mucociliary clearance.[1] Other beta agents have also been studied, and have actually been shown to increase mucociliary clearance.[2]

1. Santa Cruz R, Landa J, Hirsch J, Sackner MA. Tracheal mucous velocity in normal man and patients with obstructive lung disease: Effects of terbutaline. Am Rev Respir Dis 1974;109:458-463.
2. Wanner A. Clinical aspects of mucociliary transport. Am Rev Respir Dis 1977;116:73-125.

Goldberg: There is some work showing improvement in mucociliary function using beta-adrenergic agents.[1,2] Furthermore, a number of infants who require mechanical ventilation for treatment of respiratory distress syndrome have evidence of increased resistance, which may respond dramatically to bronchodilators.[3]

1. Wood RE, Wanner A, Hirsch J, Farrell. Tracheal mucociliary transport in patients with cystic fibrosis and its stimulation by terbutaline. Am Rev Respir Dis 1975;111:733-738.
2. Cammer P, Standberg K, Philipson K. Increased mucociliary transport by cholinergic stimulation. Arch Environ Health 1974;29:220-224.
3. Goldman SL, Gerhardt T, Sonni R, et al. Early prediction of chronic lung disease by pulmonary function testing. J Pediatr 1983; 102:613-617.

Cystic Fibrosis

David M Orenstein MD

Cystic fibrosis (CF) is the most common lethal genetic disease in white populations.[1] Although the complex of signs and symptoms that make up this syndrome has been recognized since 1938,[2] the basic biochemical defect has only recently begun to come to light.[3] CF affects virtually every organ system with epithelial surfaces—most importantly, the lungs, pancreas, intestinal mucous glands, and sweat glands. A common pathogenetic mechanism underlying the involvement of the major target systems is an alteration of ion transport across epithelial surfaces. Faulty functioning of the chloride channel of these epithelial cells leads to relative dehydration of luminal secretions.[3] These abnormally viscous secretions cause the blockage of ducts and air passages.

Genetics and Prevalence

CF is inherited as an autosomal recessive disorder. It occurs in approximately 1 in every 2,500 live births in white American and northern European populations, and in about 1 in every 17,000 births in American blacks; it is virtually unheard of in Asian populations.[4] More than 5% of the white population are presumed to be heterozygous for CF. The gene for CF is located on the long arm of Chromosome 7. The most common mutation is a deletion of phenylalanine at position 508 ("ΔF508"). This mutation apparently alters a protein product, referred to as CFTR (cystic fibrosis transmembrane regulator), that accounts for the basic defect in ion transport.[5] This particular mutation accounts for 70-80% of cases of CF.[6] More than 90 other mutations at the CF locus have been discovered, together accounting for only a small additional proportion of CF cases.[7] Prenatal testing and carrier testing can be accomplished in virtually every family having a family member with CF, using direct mutation analysis or a combination of mutation analysis and marker testing employing restriction fragment length polymorphisms.[8] Population screening for the carrier state is not yet feasible, and testing for CF in utero in the absence of a family history of CF is not useful.

Clinical Manifestations

Gastrointestinal Tract

Exocrine pancreatic insufficiency is present at birth in approximately 90% of CF patients[9] and is manifest by maldigestion of fats and protein, with consequent malabsorption, steatorrhea, and failure to thrive.[9] Patients may come to the physician with evidence of deficiencies of fat-soluble vitamins.[9] Bowel obstruction, a result of thickened intestinal mucus and pancreatic insufficiency, may be present at birth (meconium ileus) in 10% of patients,[10] or later in life (meconiumileus equivalent, now preferably referred to as distal intestinal obstruction syndrome, DIOS[9]) in 20 to 25%.[9] Rectal prolapse, caused by the same factors (and perhaps by malnutrition, with loss of musculature), is seen in 20% of CF patients in the first years of life.[11] Intussusception is much less common, but CF patients account for a significant portion of the patients with intussusception after 1 year of age.[12] Liver pathology, including nonspecific steatosis and the specific lesion, focal biliary fibrosis, is common histologically;[13] however, cirrhosis with clinically

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important manifestations such as hepatic failure or portal hypertension with hypersplenism and/or bleeding esophageal varices is, fortunately, rare.[13] Children or adults with clinically intact pancreatic function may develop acute pancreatitis.

The absence of gastrointestinal manifestations often delays the diagnosis of CF.

Sweat Glands

The chloride transport defect seen in all epithelia in CF is expressed clearly in the sweat glands, leading to the characteristic high salt content of CF sweat, and provides the basis for the sweat test (discussed later). CF patients lose more salt during exercise in the heat than do normal persons,[14] and they may experience heat prostration. Infants may be brought in for medical care with hyponatremia and hypochloremia.[15]

Respiratory Tract

The upper respiratory tract is involved in most CF patients, with radiographic evidence of pansinusitis. This is seldom clinically bothersome to the patient but occasionally is helpful diagnostically. Nasal polyps may be found in as many as 25% of these patients.[16]

The lower respiratory tract involvement in CF accounts for well over 90% of the morbidity and mortality.[1] Although the lungs are histologically normal at birth, obstructive pulmonary disease, beginning in the small airways, eventually is present in almost all patients. Recurrent cough and/or wheeze, which may be diagnosed as recurrent bronchiolitis, asthma, or pneumonia, are often the first indications of pulmonary involvement. As the disease progresses, hyperinflation, crackles, and rhonchi become apparent.

The older child (6 to 7 years and older) who is able to cooperate in the pulmonary function laboratory produces tests with a pattern of obstructive airways disease: decreased vital capacity, decreased forced expiratory volume in 1 second, decreased peak expiratory flow, and increased residual volume, indicative of air trapping.[17] These obstructive changes show varying responses to bronchodilator inhalation, with which some patients apparently improve, whereas many do not change, and others actually worsen. The response to bronchodilators is not consistent over time.[18] Exercise testing typically shows reduced exercise tolerance and fitness, with a comparatively large minute volume for the oxygen consumed, presumably because of greater than normal dead-space ventilation. Typically, a higher than normal proportion of the ventilatory capacity is required at peak work loads.

The pulmonary function and exercise tests are relatively sensitive tools for following progression of disease in the older, cooperative child.

Chronic pulmonary infection, with acute exacerbations, is characteristic of CF patients. *Staphylococcus aureus, Hemophilus influenzae*, and a variety of gram-negative organisms may be involved in the early stages, but eventually the vast majority of patients become colonized with *Pseudomonas aeruginosa*.[19] Many patients have pseudomonas at diagnosis. There seems to be a unique relationship between CF patients and pseudomonas; at least half of all CF patients are colonized with a peculiar mucoid strain of this organism that is seldom seen in other human disease states.[19,20] Recently, other organisms, such as *Aspergillus fumigatus* and *Pseudomonas cepacia*, have become increasingly important as pulmonary pathogens.[19] Despite the universal finding of chronic pulmonary colonization and infection, extrapulmonary infection is unusual, indicating that any defect in defense mechanisms is limited to the lungs. Pulmonary defenses are almost certainly inhibited by viscid mucus. Mucociliary transport rates are dramatically reduced in CF patients.[21] There may be circulating and/or locally secreted toxins that inhibit the phagocytosis and killing of pseudomonas by pulmonary alveolar macrophages and neutrophils.[22,23]

The chain of events caused by chronic infection with acute exacerbations begins with bronchiolitis and leads through bronchitis to bronchiectasis, peribronchial fibrosis, and progressive loss of pulmonary function. Figure 1 illustrates the cascade of events that lead to and result from airways infection.

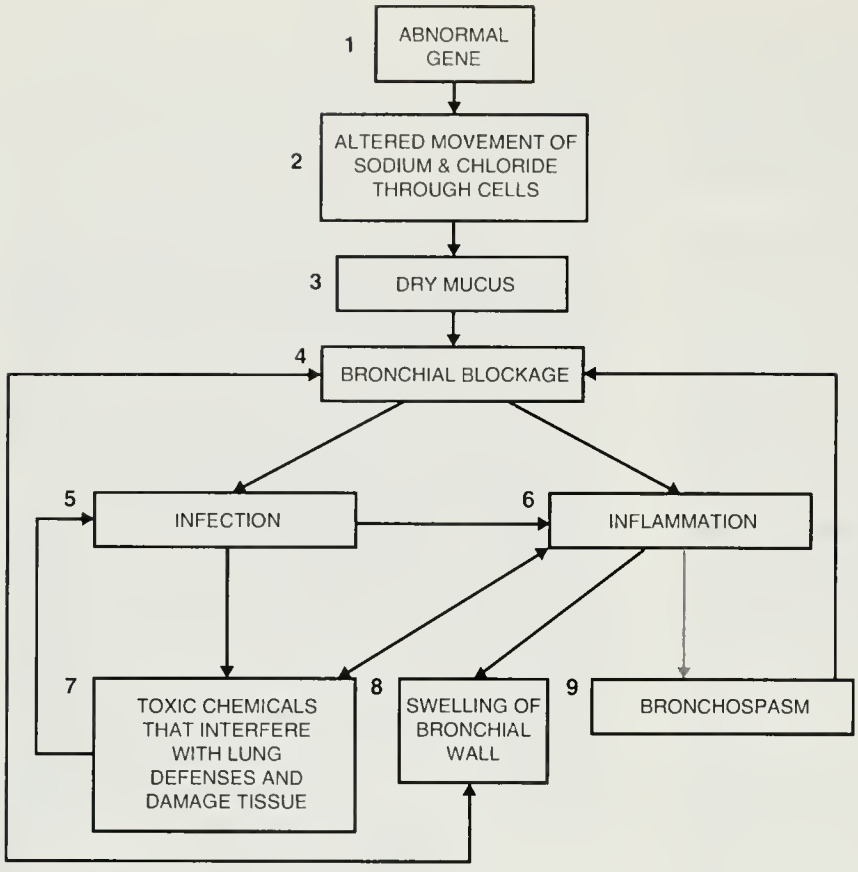

Fig. 1. The cascade of factors leading to bronchial obstruction and destruction in cystic fibrosis.(1) The abnormal gene encodes an abnormal protein that (2) alters the movement of sodium and chloride through cell walls, leading to (3) dry mucus that (4) blocks bronchioles and bronchi. With bronchial blockage, (5) infection and (6) inflammation take hold. Both infection and inflammation can cause the release of (7) toxic chemicals that interfere with lung defenses and damage tissues, thus worsening the infection and inflammation. Inflammation also causes (8) swelling of the bronchial wall, thus worsening bronchial blockage. Finally, in some individuals, inflammation may lead to (9) bronchospasm.

Pulmonary complications include pneumothorax, hemoptysis, segmental and lobar atelectasis, and pulmonary hypertension leading to cor pulmonale.

Other Organ Systems

The reproductive tract is involved in most male patients, with atresia of the vas deferens and consequent obstructive azoospermia and sterility.[24] In female patients, thick cervical mucus often results in decreased fertility.[25] Delayed puberty may be seen in either sex as a consequence of chronic illness and poor nutrition. Some adolescents and adults display a unique pattern of hyperglycemia and abnormal glucose tolerance tests, but they almost never have ketoacidosis or diabetic nephropathy or retinopathy.

Long bones and adjacent joints may be involved with hypertrophic pulmonary osteoarthropathy. Digital clubbing is a nearly universal finding in patients with even mildly abnormal lung function.

Diagnosis

Diagnosis usually must rest on the clinical features of the disease.[26] Currently, the accepted criteria for diagnosis of CF are: (1) a positive sweat test (a sweat chloride concentration greater than 60 mEq/L on a sample of at least 100 mg, obtained after maximal stimulation by pilocarpine iontophoresis), (2) chronic obstructive pulmonary disease, (3) exocrine pancreatic insufficiency, and (4) a family history of the disease.[26] Most experts require at least two of these criteria for establishing a diagnosis of CF, and the diagnosis is almost never made without a positive sweat test. Theoretically, the sweat test is simple, but false positives and false negatives are very common in tests performed outside established CF centers.[27]

It must be stressed that the key to making the diagnosis is a high index of suspicion in the presence of any of the manifestations. Table 1 lists the

Table 1. Indications for Sweat Testing*

Pulmonary Indications	Gastrointestinal Indications	Other Indications
Chronic cough	Meconium ileus, steatorrhea, malabsorption	Family history of cystic fibrosis
Digital clubbing	Rectal prolapse	Failure to thrive
Recurrent or chronic pneumonia	Cirrhosis (portal hypertension; esophageal varices)	Salty sweat; salty taste when kissed
Recurrent bronchiolitis	Prolonged neonatal jaundice	Low serum sodium or chloride; heat prostration
Mucoid pseudomonas	Hypoprothrombinemia beyond newborn period	Two positive IRT blood spot tests in newborn period
Hemoptysis	Pancreatitis	Nasal polyps
Atelectasis	Intussusception (>2 yr old)	Pansinusitis

* Modified from Reference 28, with permission. IRT=Immunoreactive trypsin

indications for a sweat test. Most physicians are sufficiently aware of the disease that few children with the triad of growth failure, steatorrhea, and chronic pulmonary disease escape diagnosis. However, atypical patients, especially those who have no clinically apparent pancreatic involvement (as many as 10% of all CF patients[9]) or who have normal growth, may escape diagnosis for years. There is no such thing as a child who "looks too good" to have CF.

Newborn Screening

An elevation of blood immunoreactive trypsin (IRT) is found in most newborns with CF.[29] The assay for IRT can be carried out on the dried blood spots obtained from newborns for routine screening (eg, for phenylketonuria and hypothyroidism). This test has been used in a number of states and countries, and its use is likely to continue. There appear to be very few false negatives with this screen, but there is a very large proportion of false positive tests.[29] This requires repeating the analysis for IRT after one positive test. If the second test still shows elevated IRT (usually at several weeks of age), definitive testing must be carried out.

Molecular genetic techniques may help establish the diagnosis in some cases. Identification of the most common CF mutation (ΔF508) is now routine through polymerase chain reaction (PCR) technology in some genetics laboratories.[8] Absence of this mutation does not rule out CF, and dozens of less common mutations are not detectable in any but a few research laboratories.

It must finally be emphasized that this is a disease in which early diagnosis and institution of an aggressive treatment program make a difference in quality and length of life.[30] Efforts at pursuing this diagnosis will be rewarded by the family's peace of mind in the case of a negative result and the knowledge of an improved outlook for the child in the event of a positive result.

Treatment

Cystic fibrosis is a complex disease, and patients require a comprehensive care program. This is usually best carried out in, or at least coordinated from, a specialized center where many different specialists are available. Therapy has three primary components: pulmonary, gastrointestinal, and psychologic.

Pulmonary Therapy

The goal of pulmonary therapy is to prevent or delay progression of the pulmonary lesion. This is

accomplished through the relief of airway obstruction and inflammation and the control of infection.

Therapy for Obstruction

Chest physical therapy (CPT) with percussion and postural drainage is the mainstay of most treatment programs,[31] despite the lack of definitive studies to indicate the ideal time for instituting this treatment or the benefits of various techniques. Most patients undergo CPT to all pulmonary segments at least once and up to four times daily, with increased frequency at the time of clinical pulmonary exacerbation.[31] Many patients have found that mechanical percussors ease this arduous task.

Exercise

Various investigators have shown aerobic exercise (jogging and swimming) to be beneficial for CF patients in terms of increased fitness and work capacity,[32] and there is some suggestion that such exercise may be as effective as traditional CPT in relief of pulmonary obstruction.[33] However, until a definitive study is available, most experts advise the use of both exercise and CPT.[33]

Aerosol Therapy

Continuous aerosol therapy came into and went out of vogue in the past 20 years with no adequate evaluation.[1] Intermittent aerosols are much more widely used but are also somewhat controversial.[1] Intermittent aerosols have been used to deliver various types of medication. Bronchodilators clearly increase airflow acutely in some patients, but they make no difference in many, and in a few they actually reduce airflow (perhaps because of a reduction in bronchomotor tone in airways kept patent only by abnormally high tone).[34] There have been no studies of the effects of long-term bronchodilator aerosol use. Mucolytic agents (eg, n-acetycysteine) are favored by many and are effective in the test tube, but they may cause irritation, bronchoconstriction, and bronchorrhea in vivo.[35] Vasoconstrictors (eg, phenylephrine) are commonly used to reduce mucosal edema, although their efficacy has yet to be established. Antibiotics (especially aminoglycosides and the anti-pseudomonas penicillin derivatives[19]) have been delivered by aerosols, apparently with favorable results.

Several experimental aerosol therapies have been introduced and await definitive study to confirm their safety and efficacy. These include amiloride,[36] which may improve epithelial chloride and sodium transport, making airway luminal contents less viscous; DNase, which can degrade neutrophil-derived DNA and therefore decrease the viscosity of airway secretions;[37] and alpha-1 antitrypsin, which may diminish the inflammatory effects of neutrophil-derived proteases.[38]

Therapy for Inflammation

Several approaches have been suggested to diminish airways inflammation in CF, including systemic steroids (alternate-day prednisone[39]) and ibuprofen.[40] Early studies have had mixed results, with apparent benefits in some patients, yet unacceptable side effects in others.[41] A definitive statement about the efficacy and toxicity of such anti-inflammatory therapy must await the results of several collaborative studies currently under way.

Therapy for Infection

There is general agreement that antibiotic treatment has probably been the single most important factor in the greatly improved prognosis in CF. Colonization and infection with staphylococcus and later pseudomonas are nearly universal, and clinical exacerbations of pulmonary disease have been convincingly linked to worsening infection. Staphylococcus and hemophilus may occasionally be eliminated from the bronchial tree in CF, but once pseudomonas colonization is established, it is almost never eradicated. It may, however, be controlled.

Antibiotic Strategies

Some CF centers advocate continuous "prophylactic" antibiotic treatment. There is some concern that this approach might lead to the early emergence of drug-resistant flora.[19] Another approach is to restrict the use of antibiotics to times of exacerbation of pulmonary disease, as evidenced by increased symptoms or signs (such as cough or sputum production),[19] or worsening chest radiograph or pulmonary function test results. Because some patients, especially those with advanced disease, will suffer exacerbations whenever they are not being treated with antibiotics, virtually continuous

treatment is occasionally indicated.[19] Still a third approach is to treat patients with full-dose drugs, based on culture results, for 2 to 3 weeks every 1 or 2 months if there is any evidence of pulmonary disease.[19] It is not clear at present which strategy is most successful.

A cornerstone of most successful treatment programs is frequent physician evaluation of patients, including bacterial examination of respiratory tract flora.[19] Oral antibiotics (dicloxacillin, cephalosporins, amoxicillin, trimethroprim with sulfamethoxazole, tetracyclines, and chloramphenicol) are often adequate when the offending organism is staphylococcus or hemophilus, and even on occasion when pseudomonas is the only organism isolated in culture.[19]

The quinolones (eg, ciprofloxacin, norfloxacin) are a relatively new class of oral antibiotics with impressive activity against pseudomonas in the lung. Because most studies have suggested that there is a rapid emergence of resistant organisms during treatment with quinolones, many experts recommend reserving their use in CF to severe exacerbations of pulmonary disease that otherwise would have prompted initiation of intravenous therapy.[42]

Intravenous antibiotics are indicated when the patient does not respond to outpatient oral administration of antibiotics.[19] The important consideration in the decision to hospitalize a patient and begin parenteral therapy is whether the child is sicker than his own baseline, and not whether the child seems dreadfully ill. It is clear that a tremendous amount of lung can be lost irreversibly while a child still looks reasonably well. Because *Pseudomonas aeruginosa* is usually the offending organism, intravenous therapy is commonly carried out with an aminoglycoside and an anti-pseudomonas penicillin or a third-generation cephalosporin.[19] Intravenous antibiotics are usually administered during hospitalization, but in carefully selected cases they may successfully be administered at home.[19]

Aerosolized antibiotics may be effective in many patients colonized with pseudomonas.[19] In those who have severe airways obstruction, aerosol penetration into the lung may be limited and render this form of treatment less valuable. Patients who cannot tolerate certain drugs (eg, colistin) intravenously may do well with the same drugs delivered by aerosol.

Lung Transplantation

Heart-lung or double-lung transplantation has been successful in a limited number of CF patients with end-stage disease.[43] One-year survival ranges from 50 to 75%. Donor-organ availability is a limiting factor for most North American lung-transplant programs, and pre-transplant mortality is very high among those on many transplant waiting lists. After transplantation, problems with organ rejection, immunosuppression, infection, finances, and psychologic adjustment require constant attention.[43] Nonetheless, some patients have had excellent results, with return to full-time work or school.[43]

Pulmonary Complications: Pneumothorax

Many pneumothoraces will eventually resolve with simple chest tube drainage but may recur at rates of 50 to 100%.[44] Therefore it is advisable to enlist some form of prevention. The instillation of chemical sclerosing agents has been used with some success.[44] In our patients, the most successful treatment for early resolution of the pneumothorax, prevention of subsequent episodes, and least morbidity has been open thoracotomy through a small subaxillary incision, permitting identification and excision of any apical blebs, stripping of the apical pleura, and manual abrasion of the remainder of the accessible pleura.[45]

The approach to pneumothorax in CF may be undergoing a change because surgical or chemical ablation of the pleural space is considered a contradindication to lung transplantation in most centers.[43]

Pulmonary Complications: Hemoptysis

Hemoptysis is a common complication and, although terrifying to patient and family, rarely is severe enough to require transfusion.[46] Deaths have been reported[47] but are exceedingly rare. Hemoptysis is thought to be the result of local infection eroding an adjacent small blood vessel. The appropriate treatment for all but the most overwhelmingly brisk bleeding is to reassure the patient and family and to initiate or continue aggressive

treatment of pulmonary infection, including chest physical therapy and antibiotics.[46] In some patients, hemoptysis may be associated with the platelet-aggregation defect seen with carbenicillin or ticarcillin therapy.[46] Because CF patients malabsorb fat-soluble vitamins,[9] treatment of hemoptysis includes supplementing with Vitamin K.[46] In the rare recalcitrant case of hemoptysis, embolization of the offending bronchial artery under radiologic guidance may bring resolution of the bleeding.[48]

Gastrointestinal Therapy

The main goal of gastrointestinal therapy is to establish good nutrition. Since pancreatic-enzyme replacement preparations and especially enteric-coated preparations became available, this once insurmountable problem has become quite manageable.[9] The correct dose of enzyme is decided by trial and error, titrating against the symptoms and signs of maldigestion and malabsorption (steatorrhea, abdominal discomfort, excessive hunger, and poor weight gain). Supplemental vitamins, especially fat-soluble A and E, should be administered at twice their recommended daily doses.[9] Diet need not be specially tailored for the CF patient as long as adequate balanced calories are supplied. Especially with good enzyme replacement, more psychologic harm than nutritional good may be done by painstaking attention to a special "CF diet," which would contribute to a patient's feeling different from family and peers.

Gastrointestinal Complications

Meconium ileus and distal intestinal obstruction (DIOS) can usually be treated with careful administration of meglumine diatrizoate (Gastrografin) enemas.[9] DIOS in its early stages may respond to large volumes of oral or nasogastric GoLytely, obviating the need for enemas.[49] Rectal prolapse is treated by gentle manual pressure on the protruding rectum and is prevented by adjustment of diet and enzymes to reduce bulky stools.[11] There is no treatment yet for the uncommon cirrhosis, but endoscopic sclcropathy may be lifesaving and may obviate the need for portocaval shunting in the rare cases of symptomatic esophageal varices.[50] Liver transplantation has been carried out in a few patients with CF, with results similar to those in non-CF liver recipients.[51] Surprisingly, pulmonary function has not worsened, and may even have improved in these CF patients after transplantation.[51]

Psychologic Considerations

The emotional burdens of a genetic, incurable, progressive, life-shortening, financially draining, and activity-limiting disease on patient and family are great. It is remarkable how well the large majority of patients and families adjust, with a very low incidence of depression.[52] Issues that patients must face include education and vocation, marriage, reproduction, medical expenses, independent living, and anticipation of disability and death. Establishing and maintaining a positive, optimistic, yet realistic attitude are extremely important. These goals are attainable, especially if the primary physician shares this attitude and maintains a close, supportive relationship with the patient and family. Knowledge of the tremendously improved prognosis over the past decades facilitates such an attitude.

Miscellaneous Treatment Considerations

Hyperglycemia occurs in a small but important group of CF patients and may require insulin therapy.[53] Salt loss may be excessive, especially during exertion in warm weather.[14] Infants may require small amounts of supplemental salt, but older children and adults will regulate their salt intake quite adequately if given free access to the salt shaker. Salt tablets are not necessary and may be harmful.

Prognosis

Almost all children with cystic fibrosis died before school age when the disease was first recognized in the late 1930s. Institution of specialized CF centers and comprehensive, aggressive treatment programs beginning in the 1950s has improved the prognosis tremendously. National median survival was 10.6 years in 1966, 20 years in 1981, and 28 years in 1989.[54] There are currently many patients in their twenties and thirties with excellent lung function, and, at the end of 1988, 21.5% of CF patients in the United States were 21 years old or older.[54] Survival probably depends on several factors, including inherent severity of

the disease, perhaps determined by genotype; aggressiveness of the treatment program as prescribed by the physician and carried out by the patient and family; and some degree of chance, especially concerning contact with various bacterial and viral pathogens. In general, the survival of male patients is better than that of females.[55] Perhaps most importantly, long-term prognosis may depend on the timing of diagnosis and institution of treatment. Several studies indicate that those CF patients who are diagnosed and who begin an aggressive treatment program before the onset of irreversible pulmonary damage have significantly better pulmonary function and survival than those discovered and treated only after considerable pulmonary tissue has been lost.[56] The recent discovery of the gene,[6] the uncovering of the basic defect,[5] and the very exciting research breakthrough of using gene-transfer techniques to cure the basic defect in CF cells in the test tube[57] have all raised hopes for improved treatments and even the possibility of a cure within the foreseeable future.

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REFERENCES

1. MacLusky I, McLaughlin FJ, Levison H. Cystic fibrosis: Part 1. Curr Probl Pediatr 1985;XV:1-49.
2. Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathological study. AJDC 1938;56:344-399.
3. Knowles MR, Stutts MJ, Yankaskas JR, Gatzy JT, Boucher RC. Abnormal respiratory epithelial ion transport in cystic fibrosis. Clin Chest Med 1986;7:285-297.
4. Klinger KW. Genetics of cystic fibrosis. Semin Respir Med 1985;6: 243-251.
5. Riordan JR, Rommens JM, Kerem B-S, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science 1989;245:1066-1073.
6. Kerem B-S, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: Genetic analysis. Science 1989;345:1073-1080.
7. Tsui L-C. International cystic fibrosis genetics consortium update, May 1991. Bethesda MD: Cystic Fibrosis Foundation.
8. Lemna WK, Feldman GL, Kerem B-S, Fernbach SD, Zevkovich EP, O'Brien WE, et al. Mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis. N Engl J Med 1990;322:291-296.
9. Park RW, Grand RJ. Gastrointestinal manifestations of cystic fibrosis: A review. Gastroenterol 1981;81:1143-1161.
10. Holsclaw D, Eckstein H, Nixon H. Meconium ileus: A 20 year review of 109 cases. AJDC 1965;109:101-113.
11. Stern RC, Izant RJ Jr, Boat TF, Wood RE, Matthews LW, Doershuk CF. Treatment and prognosis of rectal prolapse in cystic fibrosis. Gastroenterol 1982;82:707-710.
12. Holsclaw D, Rocmans C, Shwachman H. Intussesception in patients with cystic fibrosis. Pediatrics 1971;48:51-58.
13. Roy CC, Weber AM, Morin CL, LePage G, Brisson G, Yousef I, et al. Hepatobiliary disease in cystic fibrosis: A survey of current issues and concepts. J Pediatr Gastroenterol Nutr 1982;1:469-478.
14. Orenstein DM, Henke KG, Costill DL, Doershuk CF, Lemon PJ, Stern RC. Exercise and heat stress in cystic fibrosis patients. Pediatr Res 1983;17:267-269.
15. Beckerman RC, Taussig LM. Hypoelectrolytemia and metabolic alkalosis in infants with cystic fibrosis. Pediatrics 1979;63:580-583.
16. Stern RC, Boat TF, Wood RE, Matthews LW, Doershuk CF. Treatment and prognosis of nasal polyps in cystic fibrosis. AJDC 1982; 136:1067-1070.
17. Corey M, Levison H, Crozier D. Five- to seven-year course of pulmonary function in cystic fibrosis. Am Rev Respir Dis 1976;114:1085-1092.
18. Pattishall EN. Longitudinal response of pulmonary function to bronchodilators in cystic fibrosis. Pediatr Pulmonol 1990;9:80-85.
19. Thomassen MJ, Demko CA, Doershuk CF. Cystic fibrosis: A review of pulmonary infections and interventions. Pediatr Pulmonol 1987;3: 334-351.
20. Marks MI. The pathogenesis and treatment of pulmonary infections in patients with cystic fibrosis. J Pediatr 1981;98:173-179.
21. Wood RE, Wanner A, Hirsch J, Farrell PM. Tracheal mucociliary transport in patients with cystic fibrosis and its stimulation by terbutaline. Am Rev Respir Dis 1975;111:733-738.
22. Thomassen MJ, Boxerbaum B, Demko CA, Kuchenbrod PJ, Dearborn DG, Wood RE. Inhibitory effect of cystic fibrosis serum on pseudomonas phagocytosis by rabbit and human alveolar macrophages. Pediatr Res 1979;13:1085-1088.
23. Tosi MF, Zakem H, Berger M. Neutrophil elastase cleaves c3bi on opsonized pseudomonas as well as CR1 on neutrophils to create a functionally important opsonin receptor mismatch. J Clin Invest 1990;86:300-308.
24. Kaplan E, Schwachman H, Perlmutter A, Rule A, Khaw KT, Holsclaw D. Reproductive failure in males with CF. N Engl J Med 1968;279:65-69.
25. Kopito LE, Kosasky HJ, Schwachman H. Water and electrolytes in cervical mucus from patients with cystic fibrosis. Fertility Sterility 1973;24:512-516.

26. Orenstein DM. Diagnosis of cystic fibrosis. Semin Respir Med 1985; 6:252-260.
27. Rosenstein BJ, Langbaum TS, Gordes D, Brusilow SW. Cystic fibrosis: Problems encountered with sweat testing. JAMA 1978;240:1987-1988.
28. Wood RE, Boat TF, Doershuk CF. State of the art: Cystic fibrosis. Am Rev Respir Dis 1976;113:833-878.
29. Wilcken B, Brown ARD, Urwin R, Brown DA. Cystic fibrosis screening by dried spot trypsin assay: Results in 75,000 newborn infants. J Pediatr 1983;102:383-387.
30. Orenstein DM, Boat TF, Stern RC, Tucker AS, Charnock EL. The effect of early diagnosis and treatment in cystic fibrosis: A seven year study of 16 sibling pairs. AJDC 1977;131:973-975.
31. Reisman JJ, Rivington-Law B, Corey M, Marcotte J, Wannamaker E, Harcourt D, et al. Role of conventional physiotherapy in cystic fibrosis. J Pediatr 1988;113:632-636.
32. Orenstein DM, Franklin BA, Doershuk CF, Hellerstein HK, Germann KJ, Horowitz JG, et al. Exercise conditioning and cardiopulmonary fitness in cystic fibrosis. The effects of a three-month supervised running program. Chest 1981;80:392-398.
33. Orenstein DM, Henke KG, Cerny FJ. Exercise and cystic fibrosis. Physician Sports Med 1983;11:57-62.
34. Landau LI, Phelan PD. The variable effect of a bronchodilating agent on pulmonary function in cystic fibrosis. J Pediatr 1973;82:863-868.
35. Scanlin TF. Cystic fibrosis. In: Fishman AP, editor. Pulmonary diseases and disorders, 2nd ed. New York: McGraw Hill Book Co, 1998:1273-1294.
36. Knowles MR, Church NL, Waltner WE, Yanaskas JR, Gilligan P, King M, et al. A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. N Engl J Med 1990;322:1189-1194.
37. Aitken ML, Burke W, McDonald G, Villalon M, Shak S, Montgomery AB, et al. Effect of inhaled recombinant human DNase on pulmonary function in normal and cystic fibrosis patients: Phase 1 study (abstract). Am Rev Respir Dis 1991;143:A298.
38. McElvaney NG, Hubbard RC, Birrer P, Chernick MS, Caplan DB, Frank MM, et al. Aerosol alpha-1 antitrypsin treatment for cystic fibrosis. Lancet 1991;1:392-394.
39. Auerbach HS, William M, Kirkpatrick JA, Colten HR. Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. Lancet 1985;2:686-688.
40. Konstan MW, Vargo KM, Davis PB. Ibuprofen attenuates the inflammatory response to *Pseudomonas aeruginosa* in a rat model of chronic pulmonary infection. Implications for antiinflammatory therapy in cystic fibrosis. Am Rev Respir Dis 1990;141:186-192.
41. Rosenstein BJ, Eigen H. Risks of alternate-day prednisone in patients with cystic fibrosis. Pediatrics 1991;87:245-246.
42. Grenier B. Use of the new quinolones in cystic fibrosis. Rev Infect Dis 1989;11(suppl 5):S1245-S1251.
43. Scott J, Hutter J, Stewart S, Higenbottam T, Hodson M, Pemketh A, et al. Heart-lung transplantation for cystic fibrosis. Lancet 1988;2: 192-194.
44. McLaughlin RJ, Matthews WJ, Streider DJ, Khaw DT, Schuster S, Shwachman H. Pneumothorax in cystic fibrosis: Management and outcome. J Pediatr 1982;100: 863-869.
45. Spector ML, Stern RC. Pneumothorax in cystic fibrosis: A 26-year experience. Ann Thorac Surg 1989;47:204-207.
46. Stern RC, Wood RE, Boat TF, Matthews LW, Tucker AS, Doershuk CF. Treatment and prognosis of massive hemoptysis in cystic fibrosis. Am Rev Respir Dis 1978;117:825-828.
47. Holsclaw DS, Grand RJ, Shwachman H. Massive hemoptysis in cystic fibrosis. J Pediatr 1970;76:829-838.
48. Fellows KE, Khaw KT, Schuster S, Shwachman H. Bronchial artery embolization in cystic fibrosis: Technique and long-term results. J Pediatr 1979;95:959-963.
49. Koletzko S, Stringer DA, Cleghorn GJ, Durie PR. Lavage treatment of distal intestinal obstruction syndrome in children with cystic fibrosis. Pediatrics 1989;83:727-733.
50. Psacharopoulos HT, Howard ER, Portmann B, Mowat AP, Williams R. Hepatic complications of cystic fibrosis. Lancet 1981;278-280.
51. Mieles LA, Orenstein D, Teperman L, Podesta L, Koneru B, Starzl T. Liver transplantation in cystic fibrosis. Lancet 1989;1:1073.
52. Burke P, Meyer V, Kocoshis S, Orenstein DM, Chandra R, Nord DJ, et al. Depression and anxiety in pediatric inflammatory bowel disease and cystic fibrosis. J Am Acad Child Adolesc Psychiatry 1989;28:948-951.
53. Finkelstein SM, Wielinski CL, Elliott GR, Warwick WJ, Barbosa J, Wu S-C, Klein DJ. Diabetes mellitus associated with cystic fibrosis. J Pediatr 1988;112:373-377.
54. Cystic Fibrosis Foundation Data Registry Report for 1989. Bethesda MD: Cystic Fibrosis Foundation, 1990.
55. MacLusky I, McLaughlin FJ, Levison H. Cystic fibrosis. Part II. Curr Probl Pediatr 1985;15:1-39.
56. Stern RC, Boat TF, Doershuk CF, Tucker AS, Primiano FP Jr, Matthews LW. Course of cystic fibrosis in 95 patients. J Pediatr 1976;89:406-411.
57. Drumm ML, Pope HA, Cliff WH, Rommens JM, Marvin SA, Tsui L-C, et al. Correction of the cystic fibrosis defect in vitro by retrovirus-mediated gene transfer. Cell 1990;62:1227-1233.

Orenstein Discussion

O'Rourke: David (Orenstein), particularly coming from Pittsburgh, could you make a statement on the role of transplant in cystic fibrosis?

Orenstein: Our surgeons have done liver transplantations in some dozen patients with cystic fibrosis, and we reported the first nine of those in a Letter to the Editor in *Lancet* a few years ago.[1] However, I assume you're talking about lung transplantation, which is starting to be relevant to many more patients than liver transplantation. Our surgeons have now done double-lung transplants on eight patients with cystic fibrosis, and the last six have done very, very well. The surgeons in England have more experience.[2,3] They have transplanted many dozens of patients, with somewhere between 67 and 75% one-year survival. Our survival is now rivaling that, and we currently tell patients who are considering lung transplantation that they have to anticipate a 30- 50% chance of not leaving the hospital. So, I think the kinds of things that I say to patients are the kinds of things that I believe. I really believe that you are trading one disease for another. I think that the patients who do well do so for a relatively short period of time, as of right now, with this very new therapy. We don't know what awaits them several years down the line. Patients who don't do well do miserably. And yet, as I said, some of the patients for short-term are doing very, very well. But, it's really an unknown. I think it has changed life in a very positive way for quite a few patients, and it's here. There is no question that it's here. I don't know if I'm answering you satisfactorily; I think you can probably tell I'm torn. It's a very difficult issue. I think, here we are in philosophy again—part of it is that the way medical technology goes, death is unacceptable, and death is a failure, and death is the worst thing that can happen to people. Well, I don't think that death is the worst thing that can happen to people. I do think some of the people who have had just horrible post-transplant courses have had fates worse than death.

1. Mieles LA, Orenstein D, Teperman L, Podesta L, Koneru B, Starzl TE. Liver transplantation in cystic fibrosis. Lancet 1989;1: 1073.
2. Scott K, Hutter J, Stewart S, et al. Heart-lung transplantation for cystic fibrosis. Lancet 1988;2:192-194.
3. Tsang V, Madden BP, Hodson MH. Heart-lung transplantation for cystic fibrosis. Pediatr Pulmonol 1990;8(5, Suppl):256-257.

Chatburn: Could you give us your opinion on the traditional CPT regimens of postural drainage, clapping, and vibration?

Orenstein: Sure. Again, I think Dr Andersen covered this topic well. I would disagree with one thing. I think there are reasonable data to suggest, and I am referring mostly to Joe Reisman's paper[1] a couple of years ago from Toronto, that adherence to a regimen of traditional chest PT (with percussion and postural drainage), is effective in patients with cystic fibrosis. Now, what part of that does it? I agree, I don't think we know. Is it actually the clapping (the ketchup-bottle stuff) that is most important? As Dr Andersen pointed out beautifully, you can't get ketchup out of a ketchup bottle if the bottle is standing upright. Maybe it's gravity that's most important. But, I think Joe Reisman's study looked at a large number of patients, half of whom were getting traditional chest physical therapy (percussion and postural drainage) and forced expiratory technique (FET), whereas the others were only getting the FET. The ones who were getting the FET alone did considerably worse over the several-year period. I was convinced by that study. So, for the time being, although I don't know why and I don't know what part of it works, I'm convinced that it works.

1. Reisman JJ, Rivington-Law B, Corey M, et al. Role of conventional physiotherapy in cystic fibrosis. J Pediatr 1988;113:632-636.

Andersen: I must admit that it's not amazing to me that it worked out that way. What Reisman did, as far as I recall, was that he compared so-called FET with FET plus something else. What I tried to emphasize yesterday was that we need techniques working for the central airways, and we need techniques working for the periphery. What he did was that he compared some classical (not documented) techniques for clearing the periphery and central areas with techniques clearing only central areas (documented).

Rau: I have a question about the use of cromolyn sodium and steroids by inhalation. I know that good supporting evidence is lacking in the literature. What is your comment about them, and should we scrap these perhaps and just use inhaled amiloride, and is that coming?

Orenstein: One of the things that I worry about with all the research is that there are a number of very encouraging and competing areas for research including amiloride. For those of you who aren't familiar with this literature, two papers on the use of inhaled amiloride in cystic fibrosis—one by Mike Knowles and his group from Chapel Hill that appeared in the *New England Journal of Medicine* a few months ago,[1] and one from App et al in Canada and Germany that appeared in the *American Review of Respiratory Disease*[2] just a bit before that. Amiloride is a diuretic that has been around for quite some time. It affects ion transport in renal cells, and now it has been shown to do so in various epithelial cells, including respiratory ep-

ithelium, both in cell-culture and in vivo. And, it affects it in a way that partly reverses the transport abnormality in cystic fibrosis cells. What the two studies showed was that treatment with inhaled amiloride seemed to be better than treatment with placebos. The study design in the Chapel Hill paper began with a 2-week hospital admission with I.V. antibiotics and then 6 months of aerosol amiloride or placebo, measuring how quickly pulmonary function fell off over those 6 months. Pulmonary function fell off less when patients were inhaling amiloride. There is a multicenter amiloride study about to get under way that I hope will answer the questions that are raised by the fact that there were very small numbers of patients in those initial studies.

You also hear about cromolyn and steroids as inhaled agents in CF. I seem to remember a study (I can't remember where it was published), looking at cromolyn in cystic fibrosis. It was a negative study. It didn't show any improvement. Ed Pattishall has shown nicely in his analysis of negative studies in cystic fibrosis in the literature that virtually every one of those "negative" studies suffered from inadequate numbers of subjects and either inadequate or absent power analysis.[3] So, the fact that this was a negative study doesn't mean that cromolyn isn't or might not be effective in CF. I'm quite certain that there has been nothing published on inhaled steroids in CF, although the question underlying your question is, Isn't airways inflammation a very important part of the process in CF? It is a very, very important part of that process. There are several studies going on now with systemic anti-inflammatory agents, one in a national steroid study and another smaller multicenter study looking at ibuprofen. So, I think cromolyn needs to be studied, and I think steroids need more study. There are other things that are going to be studied or at least other things out there that are going to be competing for those relatively few patients to enter into studies, including things that fight the effects of mast cells. For example, there's an alpha 1-antitrypsin study, a DNase study, a study of secretory leukocyte protease inhibitor (SLPI).

1. Knowles MR, Church NL, Waltner WE, et al. A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. N Engl J Med 1990; 322:1189-1194.
2. App EM, King M, Helfesrieder R, et al. Acute and long-term amiloride inhalation in cystic fibrosis lung disease. Am Rev Respir Dis 1990;141:605-612.
3. Pattishall En. Negative clinical trials in cystic fibrosis research. Pediatrics 1990;85:277-281.

Koff: Can I jump in with one last thing? I really am glad to hear you say here at the end of the conference, mentioning yet another thing that we may be delivering by inhalation. And, genes being one of them, thank you very much, I'd prefer to keep my own. I guess what strikes me, and I think we should thank the editorial board of Respiratory Care for including their issue—I think it was November (1990)—on pentamidine and ribavirin. I think that as we go through the end of this century and start to nebulize a lot of different things that we really need to be concerned about what effect we're having on our own personnel. And, one question that sort of jumps out at me is, Isn't that something that we ought to start looking at as we deliver a lot of these different medications.

Pierson: The worlds of pediatric and adult pulmonology are in many ways separate ones, but you have nicely pointed out that, with the median survival now in the 20s, cystic fibrosis is one setting in which our worlds are going to have to intersect. And I'm interested to know how you've solved that problem. Do you let the internist into your CF clinic? Or, at what age and how do you decide when to surrender someone who has spent oftentimes his whole life under the care of a pediatrician but is now an emerging adult into the hands of somebody else?

Orenstein: Well, we're very fortunate in Pittsburgh. I think we have what is very close to an ideal situation and one that is not possible at every center. We have a wonderful adult pulmonologist who is very interested and very knowledgeable in the care of patients with cystic fibrosis. And, we have what I think is truly a gentle transition system whereby the adult pulmonologist, Dr Joel Weinberg, comes to our clinic at Children's Hospital. He sees the adult patients. He meets them at the time that they are 16 or 17, and around the time they are 18 he starts taking care of them; but, he sees them for their outpatient visits in the same setting—the same safe, familiar setting that they have been coming to for many years where they see the same nurses and a lot of the same faces. He sees them in clinic there. When and if they require hospitalization, they are hospitalized in the adult facility. He happens to be a terrific guy, which is a lot of what makes it work, but I think that is a very nice system. Before I to moved Pittsburgh 7 years ago, I had always continued to take care of my own patients through their 30s or whatever. It was not easy for me to give up those patients whom I had grown close to; and yet I recognized that there were many things about their health care when they were adults that I was not an expert in and couldn't help them with, and that they could use adult care. I really like the system at Pittsburgh; I think our patients like it, and I think they get very good care. One of the problems is we've got to be training adult pulmonologists with regard to CF and getting them excited about CF.

Pierson: Sounds like you have done a better job of it than some of the places I have heard about.

Respiratory Care of Infants and Children: Conference Summary

Richard J Martin MB BS and Robert L Chatburn RRT

This conference brought together respiratory therapists and physicians with diverse backgrounds but a common interest in developmental pulmonology as it pertains to the care of infants and children with respiratory disease. Dean Hess introduced the conference by stressing the importance of meaningful interaction between neonatal-pediatric and adult respiratory therapy practitioners. Many examples of their overlapping fields of interest can be cited. For example, physiologic derangements and management strategies for neonatal respiratory distress syndrome (RDS) and adult RDS (ARDS) have much in common despite their clearly diverse etiologies. Another example of the transmission of knowledge from infant to adult respiratory care is the evolution of continuous positive airway pressure (CPAP) from neonatal practice to the management of adult sleep apnea. Little is known of how and when childhood respiratory disease is transformed into adult lung disease, and what the role that further adverse influences like smoking may play in this progression. At this important time when the perinatal-pediatric subspecialty examination for respiratory care practitioners is being established, it must be emphasized how much adult respiratory therapists can benefit from interacting with their colleagues in the perinatal and pediatric fields.

Joe Rau gave a very complete presentation of the considerations that underlie our understanding of aerosolized drug delivery in pediatrics—including techniques for measurement of the beneficial effect in question, the pathophysiologic status of the patient, characteristics of the delivery system employed, and properties of the pharmacologic agents under study. A primary focus of his presentation was to emphasize the real paucity of information regarding the technical aspects of aerosolized drug dosing in small patients. Most data pertaining to drug delivery via metered dose inhalers, via dry powder inhalers, and during assisted ventilation with an endotracheal tube have been extrapolated from healthy and diseased adults. For example, the amount of aerosolized drug delivered through an endotracheal tube depends on such factors as rate and depth of breathing and particle size, and these factors must be considered in designing aerosol systems that will deliver adequate drug concentrations beyond the endotracheal tube and into the smaller airways and lung parenchyma of infants. The large body of recent evidence demonstrating the beneficial effect of inhaled beta-agonists on airway resistance in young patients is in marked contrast to earlier data that failed to demonstrate such a benefit, and may well be a function of the improvement in delivery systems for the pediatric patient that is occurring.

Jens Andersen from Copenhagen was able to give us a uniquely European perspective on the controversial role of chest physiotherapy in the older pediatric and adult population. He emphasized that we must demonstrate the effectiveness of techniques such as percussion and voluntary deep breathing not only in removing secretions but also in influencing the natural course of lung disease. It remains to be determined whether physiotherapy plays a meaningful role in altering the distribution of ventilation. We also need to further evaluate the role of high airway pressures, either spontaneous (as in a cough) or artificially applied, in opening

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up collapsed or blocked alveoli. Dr Andersen's unique and simple approach to the application of positive expiratory pressure (PEP) may relieve atelectasis in pediatric patients (eg, with cystic fibrosis) who are as young as 2 years of age. Its efficacy needs to be evaluated on both sides of the Atlantic.

The relative indications and contraindications of rigid and flexible bronchoscopic techniques were reviewed by Chris Green. Clearly, each technique has its advantages and disadvantages, and these must be carefully considered depending on the pathophysiologic circumstances of the patient. What clearly emerged from Dr Green's presentation and the ensuing discussion was the great skill that must be exercised in both calming the patient and administering anesthetic or sedative agents during the procedure. Bronchoscopy for the treatment of neonatal atelectasis should probably be restricted to selected patients and only performed under optimal conditions. Finally, the routine use of endotracheal suctioning appears diminished considerably in neonatal practice, in part due to bronchoscopic evidence that vigorous suctioning may contribute to airway injury.

In order to understand the rationale for various maneuvers that alter gas exchange during neonatal mechanical ventilation, Rob Chatburn utilized a model of the respiratory system based upon its mechanical properties. In this formulation, the time constant (derived from resistance and compliance) is key to ensuring adequate inhalation and exhalation of inspired gas. Such a traditional model allows classification of various ventilators in relation to their functional characteristics, although limitations of the model (such as the presence of multiple time constants) must be recognized. Current neonatal practice has largely abandoned the use of inverse I-E ratios, with renewed interest being focused on more sophisticated techniques of patient-triggered ventilation. Unfortunately, insufficient data are available to relate specific ventilator variables (such as pressure waveforms) to longer-term outcome of these infants.

Many of the basic principles of mechanical ventilation have been applied to high-frequency ventilation (HFV) by Wally Carlo, allowing HFV to become an important educational tool in neonatal ventilatory practice. Some examples of this are ensuring an adequate humidification system during HFV to prevent airway injury and ensuring that expiratory time does not become too short and result in gas trapping during HFV. The observation that gas exchange can be enhanced by HFV has been followed by several clinical trials that have failed to demonstrate a clear decrease in either mortality or bronchopulmonary dysplasia (BPD) in response to HFV. Controversy continues to surround the optimal techniques for employing both high-frequency jet ventilation and high-frequency oscillation. At this time there is no absolute indication for HFV in infants. Nonetheless, relative indications may exist—notably severe pulmonary interstitial emphysema and profound respiratory failure during conventional ventilation.

Ron Goldberg presented a model for the pathogenesis of neonatal lung injury that suggests that hyperoxia and infection may precipitate an inflammatory process via influx of polymorphonuclear leukocytes and/or macrophages. Endothelial cell injury may play a central role in this process and contribute to the vascular injury and pulmonary vasoconstriction that occurs in BPD. Lipoxygenase products, platelet-activating factor, and thromboxane are just some of the proposed mediators of this inflammatory response. Glucocorticosteroids may benefit BPD by modulating this series of inflammatory responses. Nutritional deficiency appears to interact with hyperoxia in producing an adverse outcome in animal models and probably plays a key role in the pathogenesis of BPD and the ability of these infants to fight infection. Nutritional interventions (such as early parenteral fat administration) may be useful because they may protect the developing lung from some of the injurious effects of hyperoxic exposure.

Ann Stark reviewed the available epidemiologic data that demonstrate apnea to be almost invariably present in preterm infants of less than 30 weeks gestation, but to be more likely to signify a specific clinical problem when present in close-to-term babies. A diversity of afferent inputs impinge upon the central pattern generator for respiration situated in the brain stem. Consequently, apneic episodes may have a multifactorial etiology in the premature infant. Their further classification into central,

obstructive, and mixed episodes should enhance our understanding of the underlying pathophysiologic mechanisms. Substantial data now indicate that apnea of prematurity, if resolved, is not a risk factor for subsequent sudden-infant-death syndrome (SIDS). It follows that routine home monitoring of asymptomatic preterm (and term) infants is not indicated. The discussion following this presentation was entirely supportive of a very conservative approach to pneumograms and home monitoring. Although persistent apnea may occasionally need prolonged theophylline therapy, home monitoring should only be encouraged as a last resort.

Since the first successful outcome for neonatal extracorporeal membrane oxygenation (ECMO) in 1975, over 4,000 neonates have been treated, with an approximately 80% survival. Pearl O'Rourke acknowledged that this technique is now accepted therapy for a select group of mature neonates who meet the rigid ventilatory and blood-gas criteria set for these patients. Although ECMO is successful for most subjects, real complications are possible—notably prolongation of mortality, longer-term neurologic injury, and acute procedural catastrophies. Despite Dr O'Rourke's own valiant attempts, few randomized ECMO trials employing conventional statistical techniques have occurred. The ensuing discussion reflected differences in opinion as to whether future clinical trials of neonatal ECMO can ever be accomplished. Progress might include the development of heparinized circuits, more frequent carotid artery reconstruction, the use of venovenous ECMO, and the application of ECMO to older children with adult respiratory distress syndrome (ARDS) and in cardiac disease as a bridge to transplantation. There appears to be an important role for respiratory therapists in the deployment of ECMO in neonatal and pediatric patients.

Alan Jobe reviewed the current status of neonatal surfactant therapy, which has now clearly been shown to reduce mortality from RDS by as much as 50%. Available data indicate that surfactant administration can probably be delayed beyond the delivery room, until there is early evidence for the development of RDS. The dominant clinical response is an improvement in P_{aO_2} secondary to recruitment of lung volume, while compliance and P_{aCO_2} may not simultaneously improve. Biochemical findings indicate that surfactant is largely recycled in the newborn, rather than being catabolized as in the adult; this recycling process may contribute to the relatively sustained response to only a few doses. In the neonate with RDS, surfactant is not only deficient but also relatively ineffective, probably secondary to its inactivation by proteinaceous pulmonary edema fluid. Future interest may well focus on the reevaluation of aerosolized surfactant preparations, which appear physiologically effective in animal models. Interest should also continue to be directed towards the role of surfactant therapy in other disease states in infants. Finally, we need to determine why surfactant is ineffective in a minority of preterm infants with respiratory distress.

Avroy Fanaroff reviewed the key considerations that constitute newborn follow-up. Perinatal and environmental risk (eg, socioeconomic status and maternal education) are confounding issues that must be recognized in evaluating neonatal outcome. Furthermore, data from geographic regions, rather than individual centers, are more meaningful but also almost nonexistent. In evaluating neurodevelopmental handicap in NICU survivors, a 'functional' classification of handicap may be more meaningful than an absolute number derived from a developmental scale. Growth failure (eg, decreased head size after about 8 months) and prolonged oxygen dependence are both predictors of greater handicap. Up to 50% of very-low-birthweight infants of < 1.5 kg may be oxygen dependent at 28 days. Once ventilator dependence exceeds 90 days, a bad outcome is quite likely in the low-birthweight survivor of neonatal respiratory disease. Meanwhile, follow-up must also focus on other specific patient groups and therapies (such as infants with persistent fetal circulation, or persistent pulmonary hypertension of the newborn) in whom an adverse outcome is not uncommon.

The transport of high-risk pediatric patients was reviewed by John Salyer. The pros, cons, and relative safety of ground versus air transportation were discussed. Composition of the transport team varies between centers, and respiratory care practitioners appear to be team members in about 50% of transport services. Qualifications for participation in this activity need to be enforced,

including prior PICU and NICU experience and the ability to participate in transport with sufficient frequency. Fundamental equipment guidelines are essential for this service, and personnel must be competent to continually reassess severity of the patient's clinical status. The group was reminded that intrahospital transports must be handled as skillfully as those from outside institutions. Finally, the participation of respiratory therapists in transport may be limited by the number of available personnel, and this issue requires a firm commitment on the part of the respiratory care staff.

In reviewing bronchial hyperreactivity in infants and children, Tom Hazinski addressed the role of neural transmitters on airway smooth muscle and the complex effects that may result from release of multiple neural agents at the neuromuscular junction. Cold air stimulation and histamine inhalation are both standard stimuli for assessing bronchial hyperreactivity. Application of positive pressure to the chest and negative pressure to the airway are newer techniques being used to assess flow-volume curves. Controversy has surrounded the effect of maturation on development of airway reactivity, but current data suggest that airway hyperreactivity is probably not a feature of normal infants and children. However, prematurity and the presence of BPD clearly predispose to bronchial hyperreactivity. Although increased airway smooth-muscle tone is generally considered harmful, in some conditions (eg, tracheomalacia) enhanced bronchonstrictor tone may be helpful. Furthermore, there may have been overemphasis in the past on inducing bronchodilatation with beta-agonists, when steroidal or other anti-inflammatory agents may play a useful role.

Finally, David Orenstein concluded the proceedings with an overview of cystic fibrosis (CF), and explained how this old disease has been affected by major, new scientific discoveries. Management of this disease requires a coordinated approach directed toward the patient's pulmonary, nutritional, and psychological needs. The respiratory approach must provide the means to fight airway obstruction, while preventive and therapeutic approaches must be directed against infection. Prognosis for survival in CF has continued to improve, and the full impact of the new wave of scientific discoveries has yet to be realized. With the identification and cloning of the cystic fibrosis gene in 1989, much attention is being directed towards techniques for insertion of a normal gene into these patients. Although this event is eagerly awaited, we must not let up on the intensive traditional management regimens so vital for the survival of patients with CF. This principle can probably be applied to the whole spectrum of neonatal and pediatric respiratory disease.

Neonatalogists, pediatric pulmonologists, and respiratory care practitioners alike must learn to combine traditional therapeutic approaches with the exciting techniques that are continually emerging from new scientific discoveries.

Massive Air Dissection in a Postoperative Pediatric Patient

Patrice K Benjamin RRT, Noah D Perlman RRT, and John E Thompson RRT

A 4-year-old girl with subglottic stenosis was transferred to the general ward following the surgical closure of a persistent tracheocutaneous fistula. She had required tracheostomy at age 1 month after an 11-day course of ventilation for meconium aspiration pneumonia. She had been successfully decannulated at age 2 years, but a persistent, well-epithelialized fistula remained.

Upon arrival on the floor, after surgery for closure of the fistula, the patient was alert and oriented. Soon after, while in the bathroom, she had what her parents described as a coughing spell followed by what appeared to be upper-airway obstruction and respiratory arrest. At this time, the nurse noted massive facial and neck puffiness.

The resuscitation team was alerted and bag-mask ventilation was initiated, but proved to be difficult to perform. An uncuffed oral endotracheal tube (ETT) was then inserted; however, a large air leak from the dehisced surgical wound ensued and ventilation remained ineffective. (A cuffed ETT positioned below the tracheal defect would probably have provided an adequate airway; however, in our facility the smallest cuffed ETT stocked on the emergency cart has a 5.0-mm ID, which would have been too large for this 4-year-old child with a history of subglottic stenosis.) The ETT was quickly removed and a 2.0-mm Shiley tracheostomy tube was inserted through the surgical site. Further air leak and dissection ceased, and effective ventilation could then be provided.

Breath sounds were noted to be bilateral with wheezes. Subcutaneous air was noted from the mid-thigh to the neck and face, throughout the abdomen and chest wall. Oxygen saturation by pulse oximeter (S_{pO_2}) was initially 100%, but slowly began to drop. A portable chest radiograph was taken (Fig. 1), and the patient was transferred to the ICU. The patient's heart rate and blood pressure remained stable throughout the incident. When the child arrived in the ICU, breath sounds could no longer be auscultated, and S_{pO_2} had dropped to the low 80s in spite of manual ventilation with 100% oxygen.

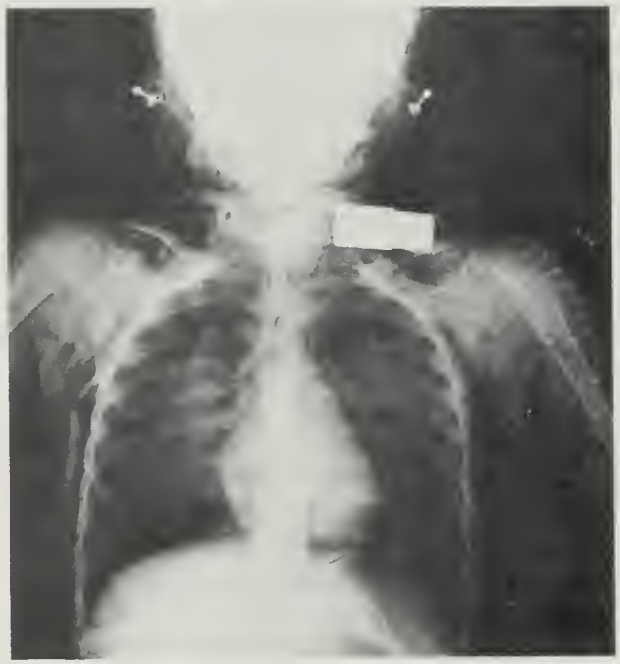

Fig. 1. Portable chest radiograph of a 4-year-old girl being mechanically ventilated via tracheostomy tube following respiratory arrest that occurred subsequent to surgical closure of a persistent tracheocutaneous fistula.

Questions

Radiographic Findings: What does the chest radiograph in Figure 1 reveal?
Etiology-Precipitating Factors: What might be the cause of the findings in the radiograph?
Treatment: What treatment is indicated?

Answers and Discussion on Next Page

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Answers

Radiographic Findings: The chest radiograph shows bilateral pneumothoraces with subcutaneous, interstitial, and intramuscular air present in the chest wall, neck, and face. A pneumomediastinum is also evident.

Etiology-Precipitating Factors: The cutaneous fistula had been repaired by a muscle-band and skin-flap closure, in the operating room. The tracheal hole was not disturbed. Postoperatively, increased intrathoracic pressures generated by either a Valsalva maneuver or coughing caused air to leak through the tracheal hole (which no longer vented through the skin) into the tissues of the neck and face. Continued coughing (and subsequent bag-mask ventilation) allowed further dissection of air through the fascial plane into the mediastinum and pleura.

Treatment: Bilateral chest tubes were inserted, and S_{PO_2} subsequently increased to the 90s. Throughout this procedure, the patient was manually ventilated with 100% oxygen. Within minutes of chest-tube insertion, the patient began to make weak respiratory efforts and only required assistance with an anesthesia bag for approximately 20 minutes. She was then switched to 40%-oxygen trach collar.

A follow-up chest radiograph taken within 30 minutes of the chest-tube insertion (Fig. 2) revealed complete resolution of the pneumothoraces. On exam the next morning, the subcutaneous air was dramatically decreased. The patient remained in the ICU one more day. The chest tubes were then removed, and she was transferred to the general ward on a room-air trach collar. On Postoperative-Day (POD) 5, she returned to the operating room. A bronchoscopy showed 10% subglottic narrowing (clinically unimportant in this patient) and an otherwise normal anatomy. The patient was decannulated, and a pressure dressing was placed on the stoma. No further surgical revision was performed. On POD 9, the patient's tracheostomy site was noted to have healed over, with no detectable fistula. A small amount of residual subcutaneous air remained in her anterior chest wall. She was then discharged to her home. Six weeks later she was seen in the otolaryngology clinic. By this time, complete closure of the tracheostomy site had occurred, and the child was not experiencing symptoms of airway obstruction.

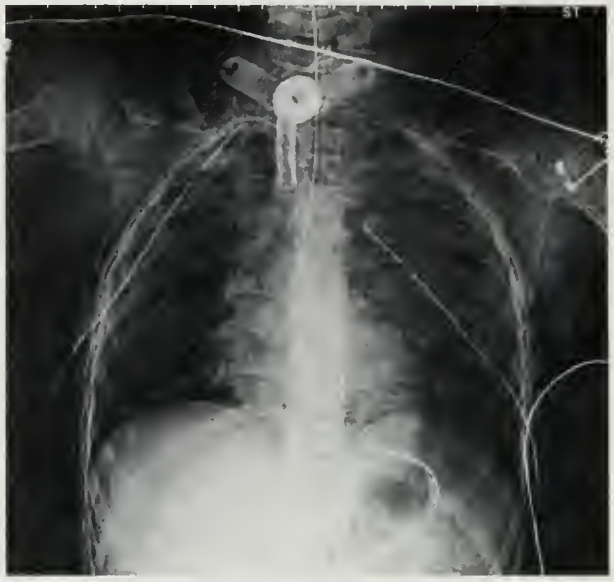

Fig. 2. Portable chest radiograph of a 4-year-old girl within 30 minutes of bilateral chest-tube insertion to treat pneumothorax.

Discussion

This presentation is unusual in that the pathway of air dissection is not the more familiar route of intra-alveolar rupture usually seen in air leak. In his classic 1939 paper,[1] Macklin described the phenomenon of air dissection following alveolar rupture. In a series of experiments on cats, he demonstrated the tracking of air along the vascular sheaths of the pulmonary vessels and its eventual convergence at the hilum and escape into the mediastinum, peritoneum, and soft tissues of the head, neck, thorax, and legs. Our patient appears to have experienced a reversal of this progression, with air leak starting in the soft tissue of the neck (as subcutaneous and interstitial air) and culminating in pneumothoraces.

The symmetry of the collapse, the lack of tracheal or mediastinal shift, the normal curvature of the diaphragms, and the patient's relative cardiovascular stability throughout the event suggests that these were not tension pneumothoraces.[2] However, the size of the pneumothoraces and the degree of patient compromise called for aggressive treatment (that is, insertion of bilateral chest tubes).

Interstitial air is an ominous sign of air leak, but in itself is not life-threatening. Our review of the literature on air-leak phenomena revealed no specific treatment for interstitial air. However, when mediastinal air causes severe cardiopulmonary compromise, decompression may be achieved through incision of the tissues above the suprasternal notch.[3] This was not necessary in our patient. Oxygen is unlikely to hasten the resolution of interstitial air unless the air leak is ongoing. In our patient, dissection of air into the tissues ceased when the tracheostomy tube was inserted.

In our patient, the air leak and dissection that precipitated the respiratory arrest is thought to have been caused by cough or the Valsalva maneuver and to have been further exacerbated by the positive-pressure ventilation provided prior to insertion of the tracheostomy tube. Immediately following tracheostomy tube insertion, breath sounds were noted to be bilateral with wheezes, suggesting that pneumothorax was not the initial sight of air leak.

There are isolated reports of free intra-abdominal air, subcutaneous air, and pneumothorax in the presence of tracheal injury without positive-pressure ventilation. In one case,[4] a 21-year-old person suffered a suprajugular gunshot injury resulting in a tracheal wall defect. A chest radiograph revealed bilateral pneumothoraces, pneumomediastinum, pneumoretroperitoneum, pneumoperitoneum, and marked subcutaneous emphysema of the chest and abdominal wall. In another case,[5] a 28-year-old person suffered blunt chest trauma in an auto accident. Subcutaneous emphysema, pneumomediastinum, and pneumoperitoneum were seen on chest radiograph. Bronchoscopy revealed a tear in the membranous trachea. In this case, the clinicians noted that although pneumoperitoneum is rarely secondary to extra-abdominal injury it can be a presenting sign of tracheal disruption.

The incidence of tracheocutaneous fistula in decannulated children has been reported to be anywhere from 3.3% to 29%.[6] These fistulas are caused by growth of thick epithelium along the tracheostomy tract. Three methods of surgical repair are recommended:[6] (1) primary closure of the site, (2) excision of the fistulous tissue followed by primary closure, and (3) excision of fistulous tissue with a brief period of recannulation. In Method 1, a simple muscle flap and skin closure is performed. In Method 2 the fistulous tract is excised down to the trachea, the tracheal defect is repaired, and muscle and skin-flap closure is performed. In Method 3, the fistulous tract is excised down to the trachea followed by a brief period of recannulation to effect healing by secondary intention (that is, by granulation that forms from the base and sides toward the surface of the wound).

In one study of 15 children with tracheocutaneous fistulas, surgical repair was performed using Method 1 in two children, Method 2 in four, and Method 3 in nine. The only complication associated with Method 1 was wound infection in one patient. Complications associated with Method 2 included persistent stridor; respiratory distress; and in one patient subcutaneous air, pneumomediastinum, and pneumothorax requiring immediate recannulation. This patient's air dissection followed a paroxysmal coughing spell in the operating room. No complications were associated with Method 3.

Initially in our patient, Method 1 was used; it was believed that surgical repair of the tracheal defect was contraindicated because closure might result in increased tracheal stenosis. However, because of the development of air leak and dissection and respiratory arrest, recannulation became necessary, and the tracheocutaneous fistula ultimately healed by secondary intention.

Our case demonstrates an unusual variant of the phenomenon of air leak. It is important to note that just as air may escape the lung through alveolar rupture and track along vascular sheaths to cause pneumothorax, pneumomediastinum, and subcutaneous emphysema, so may it track in the opposite direction if provided the opportunity. This case reinforces an important fact for clinicians: Massive air leak and air dissection may occur in the absence of mechanical ventilation, and the source need not always be alveolar rupture. Whenever surgery is performed on the pediatric airway, the clinical staff must anticipate potential complications and be prepared to provide appropriate emergency intervention.

REFERENCES

1. Macklin CC. Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum. Arch Intern Med 1939;64:913-926.

2. Sahn SA, ed. Pulmonary emergencies. New York: Churchill Livingstone, 1982:253,255,267.
3. Sahn SA. Pneumothorax and pneumomediastinum. In: Mitchell R, Petty T, eds. Synopsis of pulmonary disease. St Louis: CV Mosby, 1982:201.
4. Brinkmann M, Singbartl G, Jaspers-gen-Bunger U. Free intraabdominal air following an isolated gunshot injury to the trachea. Anaesthesist 1990;39:113-116.
5. Barnhart GR, Brooks JW, Kellum JM. Pneumoperitoneum resulting from tracheal rupture following blunt chest trauma. J Trauma 1986;26:486-487.
6. White AK, Smitheringale AJ. Treatment of tracheocutaneous fistulae in children. J Otolaryngol 1989;18:49-52.

CORRECTIONS

In Table 2 of "Enhanced Capabilities of Current ICU Ventilators: Do They Really Benefit Patients?" Respir Care 1991;36:362-376, the values for $\dot{V}_I$ and peak spontaneous $\dot{V}_I$ are shifted too far to the left. A correct version of the table is

Table 2. Comparative Ranges of Operation for Two Current Ventilators and Their Non-Microprocessor Predecessors*

	Ventilators			
	Puritan-Bennett		Bear Medical	
Variables	MA-1	7200	Bear 1	Bear 5
V_T (mL)	100-2200	100-2500	100-2000	50-2000
$\dot{V}_I$ (L/min)	5-100	10-120	10-120	5-150
f (breath/min)	6-60	0.5-70	0.5-60	0.5-150
PIP (cm H_2O)	80	120	100	150
PEEP (cm H_2O)	15	35	30	50
Peak spontaneous $\dot{V}_I$ (L/min)	100	180	100	150

* All data obtained from manufacturers' literature.

In Figure 13 of "How Should Bronchodilators Be Administered to Patients on Ventilators?" Respir Care 1991;36:377-394, the photograph is upside down.

In Figure 2 of Test Your Radiologic Skill: "Can the Pressure Tracings Be Trusted?" Respir Care 1991;36:435-437, the chest radiograph appears in a reversed position under the arrow and dotted line. Correct placement of the radiograph is

We regret these errors
and apologize
to both authors and readers
for this inconvenience.

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Choose the single, most correct answer.

The issue and page number of the paper to which the question applies are given in brackets [ ] following the question.

1. Which of the following is most correct?
   a. A closed-circuit calorimeter is ideally suited for the patient on assist-control or control ventilation at an $F_{IO_2} < 0.60$.
   b. Indirect calorimetry is the calculation of heat production through the measurement of pulmonary gas exchange.
   c. If FRC falls during indirect calorimetry, $\dot{V}_{O_2}$ will be overestimated.
   d. Open-circuit calorimeters use the volumetric-loss or replenishment techniques.
   e. b and c only

[July 90:640-659]

2. Which of the following is most correct?
   a. FRC is believed to be the most 'natural' and reproducible lung volume.
   b. The radiographic approach is well suited for monitoring lung volumes in mechanically ventilated patients.
   c. In open-circuit techniques used to measure FRC, the indicator gas may be helium, nitrogen, carbon monoxide, or sulfur hexafluoride.
   d. all of the above
   e. a and c only

[July 90:660-668]

3. Which of the following is most correct?
   a. During machine-assisted ventilation, muscle contraction continues throughout most of inspiration when the patient is dyspneic.
   b. Paralysis often increases the functional compliance of the chest wall.
   c. A large hydrothorax accentuates the vertical gradient of pleural pressure.
   d. all of the above
   e. a and b only

[July 90:669-696]

4. Which of the following is most correct?
   a. Devices placed around the torso to monitor respiratory movements include mercury-in-silastic strain gauges, doppler flow detectors, and magnetometers.
   b. Feeble respiratory efforts during obstructive events may be misinterpreted as central events if torso monitors of respiration alone are relied upon.
   c. The impedance pneumograph can reliably distinguish the chest motion that occurs during an obstructive event from an actual event.
   d. a and b only
   e. b and c only

[July 90:697-708]

5. Which of the following is most correct?
   a. The Korotkoff method of blood-pressure determination uses Riva-Rocci sounds.
   b. The upper bladder of the oscillotonometer is the occluding bladder.
   c. Noninvasive methods to determine cardiac output include the dilution method and the CO_2 rebreathing method.
   d. all of the above
   e. a and b only

[July 90:709-718]

6. Which of the following is most correct?
   a. Systems that allow a designated group of physicians to control utilization of respiratory care services have been shown to reduce inappropriate or unnecessary therapy.
   b. Operating costs of a noninvasive monitor can be attributed to reductions in labor intensity, conservation of other resources, and improved quality.
   c. It has been shown that 14-30% of ICU admissions are to provide increased monitoring, not to provide active treatment.
   d. all of the above
   e. a and c only

[July 90:728-739]

7. In the study by Gray, MacIntyre, and Kronenberger, suctioning with normal-saline instillation (NSI)
   a. resulted in greater patient discomfort than suctioning without NSI.
   b. appeared to enhance secretion removal primarily through cough stimulation.
   c. resulted in bradycardia in the majority of patients.
   d. all of the above
   e. a and b only

[August 90:785-790]

8. In the study by Kollef and Johnson,
   a. the effect of nasal gas flow on dyspnea in critically ill adults was evaluated.
   b. a significant increase in dyspnea was observed after induction of nasal anesthesia.
   c. the reduction in dyspnea during tracheal gas flow appeared to be a placebo phenomenon caused by the wearing of the transtracheal catheter.
   d. the perception of dyspnea was significantly influenced by tracheal gas flow.
   e. c and d only

[August 90:791-799]

9. In the study by Hess and Spahr,
   a. little variation was observed between volumes delivered by various brands of resuscitators.
   b. ill-fitted gloves were observed to affect resuscitator volume delivery.
   c. a significant increase in delivered volume occurred as hand size increased but not when two hands were used (instead of one) to squeeze the bag.
   d. the importance of using two hands during bag-valve ventilation was re-emphasized.
   e. a and d only

[August 90:800-805]

10. Which of the following is most correct?
    a. The Pendelluft is a German piston oscillator that has been used in HFOV studies.
    b. HFOV in particular has been associated with necrotizing tracheobronchitis.
    c. Hummingbirds synchronize wing-beat with respiration and probably facilitate diffusion in a manner similar to HFOV.
    d. During HFFI, an active negative 'pull' stroke aids expiration.
    e. all of the above

[August 90:815-830]

11. In their study of mechanically ventilated patients in a children's hospital ICU, Benjamin et al found
    a. ventilator failures occurred more frequently than did alarm failures or circuit problems.
    b. a statistically significant increased incidence of pre-necrosis occurred in nasally intubated patients compared to orally intubated patients.
    c. no association between mortality and ventilator complications.
    d. all of the above
    e. b and c only

[September 90:873-878]

12. According to a survey conducted by Salyer and Chatburn, de facto standards in perinatal-pediatric respiratory care include
    a. continuous measurement of F_{IO_2} in oxygen hoods.
    b. routine use of auxiliary continuous airway-pressure monitors with time-cycled pressure-limited neonatal ventilators.
    c. q4-hour measurement of ventilator F_{IO_2}.
    d. all of the above
    e. a and b only

[September 90:879-888]

13. In Tiffen et al's study of a single-lumen insufflating suction catheter, positive and negative pressures generated within the test lung increased as
    a. the ratio of suction-catheter outer diameter to ET-tube inner diameter (SC:ETT) increased.
    b. the suction catheter outer diameter increased and the SC:ETT and insufflating flow remained constant.
    c. insufflating flow decreased and SC:ETT remained constant.
    d. all of the above
    e. a and c only

[September 90:889-897]

14. Which of the following is most correct?
    a. During MVV ventilation, ventilators use algorithms to adjust either ventilatory frequency, tidal volume (level of PSV), or inspiratory flow.
    b. If MVV ventilation is used to wean a patient from mechanical ventilation, it may be necessary to set the target V_E at a level that will result in mild hypoventilation.
    c. During MVV ventilation, adjustments in the level of ventilatory support delivered to the patient are automatically made without clinician intervention.
    d. a and c only
    e. b and c only

[September 90:898-905]

15. In the evaluation of the MAX Transport ventilator, which of the following observations was (were) made?
    a. Measured V_T at a set V_T increased as test-lung compliance was reduced.
    b. Measured V_T at a set V_T decreased as test-lung compliance was reduced.
    c. Measured V_T at a set V_T of 1.0 mL was decreased as frequency was increased.
    d. Both a and c are correct.
    e. Both b and c are correct.

[October 1990:952-959]

16. Which of the following statements is (are) true?
    a. The four mycoses endemic to specific geographic areas of the U.S. are histoplasmosis, blastomycosis, coccidiodomycosis, and candidiasis.
    b. The systemic antifungal drugs available in 1990-1991 are Amphotericin B, fluocytosine, ketoconazole, and ciprofloxacin.
    c. The drugs recommended for systemic mycotic infections are very safe and produce few side effects.
    d. Amphotericin B is the drug of choice for aspergillosis, mucormycosis, sporotrichosis, and histoplasmosis.
    e. Both a and d

[October 1990:987-989]

17. According to the review by Vakharia and Hall, early signs indicative of malignant hyperthermia include *all but*
    a. A rise in $P_{et}CO_2$
    b. Increased blood pressure
    c. Muscle rigidity
    d. Overt seizure activity
    e. Both c and d

[October 1990:978-986]

18. According to the review by Vakharia and Hall which of the following is (are) true?
    a. Susceptibility to malignant hyperthermia (MH) is genetically transmitted but prior identification is impossible
    b. Intravenous dantrolene should be administered within minutes of a diagnosis of probable MH.
    c. MH victims require hyperventilation and high oxygen concentrations.
    d. All of the above
    e. b and c only

[October 1990:978-986]

19. Time weighted average (TWA)
    a. is a way of estimating a subject's exposure to a given substance during a workday.
    b. is equivalent to the No Observed Exposure Level (NOEL).
    c. is always 2.7 $\mu g/m^3$.
    d. all of the above
    e. a and c only

[November 1990:1042-1048]

20. Which of the following is incorrect?
    The environmental level of ribavirin
    a. has been reported to be highest when the drug is administered by simple oxygen tent alone.
    b. can be maintained at an acceptable level when administered via mechanical ventilator equipped with appropriate filters.
    c. has been deemed acceptable when a caregiver's time-weighted average can be shown to be ≤ 2.7 $\mu g/m^3$.
    d. is inversely proportional to the patient's serum level
    e. both c and d

[November 1990:1042-1048]

21. With pressure support ventilation, factors that could increase the patient's work of breathing include
    a. ventilator insensitivity
    b. inadequate inspiratory flow
    c. absence of auto-PEEP
    d. all of the above
    e. a and b only

[November 1990:1049-1055]

22. When ventilator flow matches patient demand
    a. the inspiratory cycle is prematurely terminated.
    b. patient-ventilator dyssynchrony is likely.
    c. work of breathing is reduced.
    d. peak inspiratory pressure is increased.
    e. both c and d

[November 1990:1056-1064]

23. In a group of patients randomly selected to receive low-flow oxygen either dry or humidified by a bubble humidifier,
    a. epistaxis was a frequent complication in patient's receiving dry oxygen.
    b. significant differences in complications were seen between the two subgroups.
    c. all patients were examined daily and asked standard questions about the presence of dry nose, dry throat, headache, chest discomfort, and change in sputum production.
    d. results suggested that possible complications offset potential savings.
    e. b and d only

[Respir Care 1980:25:1143-1144. Reprinted in December 1990:1265-1266]

24. In the study by Blanchette et al,
    a. no difference in the P_{lcO_2}-P_{aO_2} relationship was identified based on gestational age, postnatal age, or pH.
    b. sensitivity referred to the ability of pulse oximetry (S_{pO_2} within specified limits) to detect hypoxemia or hyperoxemia.
    c. hyperoxic episodes were limited to near 3% and hypoxemic episodes to 4% when S_{pO_2} was maintained between 92% and 96%.
    d. all of the above
    e. b and c only

[January 91:25-32]

25. In the study by Godwin et al, sputum induction by ultrasonic nebulization to diagnose *Pneumocystis carinii* pneumonia
    a. proved to have a sensitivity of 83% in HIV-positive patients.
    b. induced bronchospasm in 10% of the patients.
    c. proved to have a specificity of 69% in HIV-negative patients.
    d. all of the above
    e. a and c only

[January 91:33-39]

26. Which of the following is most correct?
    a. The index of patient effort used by Nishimura is the product of inspiratory pressure and rate.
    b. The end-expiratory-plateau technique formeasuring auto-PEEP is accurate only if the ventilatory muscles are relaxed during expiration.
    c. Flow-triggering mechanisms appear to impose more work of breathing than do pressure-triggering mechanisms.
    d. all of the above
    e. a and b only

[January 91:45-51]

27. The inhalation technique, described by Johannigman and Branson,
    a. is used with an oxygen enrichment device (OED) during mouth-to-mouth resuscitation.
    b. when used in combination with the OED, provided an increase in F_{DO_2} compared to standard techniques of mouth-to-mask resuscitation.
    c. when used in combination with the OED, resulted in augmentation of tidal volumes compared to standard techniques of mouth-to-mask resuscitation.
    d. all of the above
    e. a and b only

[February 91:99-103]

28. Which of the following is most correct?
    a. Under clinical conditions, disinfectants become inadvertently diluted during reuse.
    b. Gluteraldehyde vapors may cause allergic or even toxic reactions.
    c. Semicritical equipment should be disinfected of virtually all non-spore-forming pathogens including mycobacteria.
    d. all of the above
    e. a and c only

[February 91:104-109]

29. In their study of 10 manual resuscitators, Barnes and Stockwell found that
    a. patient-valve backward leakage did not occur at -18°C and 50°C.
    b. at extremely cold ambient conditions, manual resuscitators with bag-type reservoirs delivered higher F_{DO_2}s than did resuscitators with tube-type reservoirs.
    c. only the Code Blue and DMR resuscitators met ASTM and ISO standards across the operational temperature range of -18°C to 50°C.
    d. all of the above
    e. a and c only

[March 91:161-172]

30. According to Shigeoka,
    a. the threat of rapid obsolescence may explain why investigators have been reluctant to perform long-term field studies of demand valves.
    b. the Medicare half-rate provision for oxygen flows < 1 L/min encourages the use of transtracheal catheters and reservoir conservers.
    c. the use of oxygen conservers could result in reduced operating expenses for vendors and increased ambulation for patients.
    d. all of the above
    e. a and c only

[March 91:178-183]

31. According to Stoller, when attempting to establish clinical unweanability
    a. one should review remedial aspects of the patient and the ventilator system and optimize the likelihood of successful weaning.
    b. the clinician poses the question: Of those patients predicted not to wean on the basis of a weaning parameter, how many fail to wean?
    c. weaning parameters that help to establish unweanability should have high negative predictive values.
    d. all of the above
    e. a and b only

[March 91:186-198]

32. Which of the following is most correct?
    a. A ventilator-dependent patient's need for a second complex technology is usually an indication that foster care should be provided.
    b. Chronic ventilator care outside of the U.S. has focused on postpoliomyelitis patients, high quadriplegics, and patients with neuromuscular disease.
    c. In the U.S., home mechanical ventilation has been most successful in patients with COPD and neuromuscular disease.
    d. all of the above
    e. b and c only

[March 91:199-204]

33. According to Gilmartin,
    a. patients with amyotrophic lateral sclerosis are easily managed on home ventilation.
    b. weaning from a critical-care ventilator on CPAP and/or a pressure-support mode can easily be continued at home.
    c. home care services need to be involved early in the hospital-discharge planning process.
    d. all of the above
    e. a and b only

[March 91:205-216]

34. Theophylline
    a. is taken by an estimated 10 million asthmatic Americans.
    b. should be injected quickly, within 20 minutes.
    c. might be responsible for causing some cases of apnea of prematurity.
    d. all of the above
    e. b and c only

[March 91:218-221]

35. Of the portable suction systems evaluated by Curran et al
    a. none had a pressure regulator as a component.
    b. only two could generate a maximum pressure equal to standard suction pressure (120-150 torr).
    c. all suctioned the same amount of maple syrup in 5 seconds as did wall suction.
    d. all of the above.
    e. b and c only

[April 1991:259-266]

36. The use of a malleable metal intubation stylet
    a. allows shaping of the endotracheal tube and can aid in its insertion.
    b. permits the forceful tube insertion desirable in emergency intubations.
    c. is safe as long as the distal end of the stylet barely protrudes beyond the end of the endotracheal tube.
    d. all of the above
    e. a and c only

[April 1991:267-269]

37. According to the critical review of the literature by Eid et al, chest physiotherapy
    a. probably is not helpful and may be harmful in uncomplicated pneumonia.
    b. appears to be helpful in the management of bronchiolitis.
    c. is indicated in all routine postoperative management.
    d. all of the above
    e. a and b only

[April 1991:270-282]

38. According to the critical review of the literature by Eid et al, in bronchiectasis
    a. mucociliary clearance is usually preserved.
    b. chest physiotherapy does not enhance secretion clearance.
    c. chest physiotherapy may enhance secretion clearance but is not associated with documented improvement in pulmonary function.
    d. distorted bronchi can be returned to normal with secretion removal and antibiotics.
    e. a and b only

[April 1991:270-282]

39. According to the lecture by Dr Mary Ellen Avery
    a. at least 30,000 infants worldwide have been treated with synthetic or natural surfactant.
    b. the method of choice for surfactant administration in 1991 is aerosolization.
    c. administration of only a small amount of surfactant (3-5 mL) can reduce surface tension in the lungs of a premature infant.
    d. all of the above.
    e. a and c only

[April 1991:283-287]

40. Evidence contributing to the concept that respiratory muscle fatigue may be involved in failure to wean includes
    a. electromyographic (EMG) and clinical evidence of diaphragm dysfunction has been shown to precede hypercapnia in patients who fail to wean.
    b. rapid, shallow spontaneous breathing characterizes those who fail to wean.
    c. patients with increased WOB are more likely to fail to wean.
    d. all of the above
    e. b and c only

[April 1991:290-296]

41. Valid, clearly defined criteria for elective ventilation
    a. have been determined by prospective controlled studies.
    b. might include the presence of confirmed obstructive ventilatory impairment.
    c. might include a history of symptoms suggestive of sleep-related alterations in gas exchange.
    d. should be completely independent of patient prognosis
    e. both b and c

[April 1991:297-304]

42. In the bench study by Rau and Shelledy
    a. a decelerating flow pattern produced the highest and an accelerating pattern the lowest peak inspiratory pressure.
    b. the lowest mean airway pressure was produced by an accelerating flow pattern.
    c. the lowest mean inspiratory pressures are produced by a decelerating flow.
    d. under low-compliance conditions a direct relationship exists between peak and mean pressures.
    e. under low-compliance conditions as peak pressure decreases, mean pressure decreases.

[May 1991:347-356]

43. According to Branson's review
    a. A number of evaluations suggest that current ventilators reduce patient work of breathing more than did many older ventilators.
    b. The benefits of inspiratory flow pattern control have been clearly demonstrated in numerous studies.
    c. APRV has been shown, clearly and unequivocally, to improve gas exchange and hemodynamic status in mechanically ventilated patients.
    d. New-generation mechanical ventilators incorporate well-validated respiratory mechanics monitors that have been clearly demonstrated to be valuable in patient management.
    e. Contrary to expectations, pressure support ventilation may disrupt patient-ventilator synchrony.

[May 1991:362-376]

44. According to Tobin, important factors that can contribute to innominate artery rupture include
    a. pressure erosion by an overinflated endotracheal tube cuff.
    b. tracheal wall erosion by the tip of an excessively long tube
    c. gastroesophageal reflux
    d. portal hypertension
    e. a and b only

[May 1991:395-406]

45. Factors present in neonates and infants that can cause drug pharmacokinetics and pharmacodynamics to differ from those found in adults include
    a. decreased gastric emptying time, high gastric pH, and increased intestinal transit rate
    b. relatively lower volume of distribution
    c. relative pancreatic hyperactivity
    d. all of the above
    e. both a and b

[June 1991:514-542]

46. According to Green's review
    a. Flexible bronchoscopy is superior to rigid bronchoscopy for evaluating a case of suspected epglottitis.
    b. The distal bronchi can be more readily observed with the flexible than with the rigid bronchoscope.
    c. Airway dynamics can be more readily observed with the rigid than with the flexible bronchoscope.
    d. a and b
    e. b and c

[June 1991:555-565]

47. According to the review of Coghill et al
    a. HFJV employs a high pressure source to deliver a volume of gas through a small-bore injector cannula.
    b. HFFI provides small volumes at high frequencies by interrupting a gas flow (no injector cannula is used).
    c. HFOV differs from other forms of HFV because expiration is active.
    d. HFPPV usually employs a conventional positive-pressure ventilator.
    e. all of the above

[June 1991:596-612]

48. According to Chatburn's review
    a. In general, a surfactant-deficient lung is more likely to develop PIE than is a more easily expanded lung.
    b. Collateral gas flow (through the pores of Kohn, canals of Lambert, and interbronchiolar channels of Martin) is lacking in the immature lung.
    c. When the ventilatory muscles are relaxed, measurements of pressure, volume, and flow can be used to calculate total respiratory system compliance and resistance using the equation of motion.
    d. All of the above
    e. a and b only

[June 1991:569-592]

49. In neonates, which of the following is (are) true:
    a. Diuretic usage can result in hypokalemia, hyponatremia, hypochloremia, and hypercalciuria.
    b. Diuretic usage can lead to decreased airways resistance, decreased dynamic compliance, and decreased specific conductance.
    c. Bronchodilator therapy can reduce airways resistance and work of breathing.
    d. all of the above
    e. a and c only

[June 1991:613-620]

50. According to Andersen's review
    a. All postoperative patients should receive chest physiotherapy, PEP mask therapy, or incentive spirometry.
    b. Early ambulation of the surgical patient is probably the most effective method of normalizing pulmonary function.
    c. Studies of PEP therapy suggest that oxygen tensions may decrease and airway function deteriorate during such therapy.
    d. all of the above
    e. both b and c

[June 1991:546-554]

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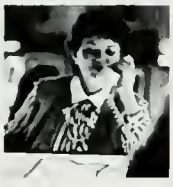

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Calendar of Events

AARC & AFFILIATES

July 10-12 in Houston, Texas. The TSRC meeting features AARC President Patrick Dunne, and Kevin Shrake, Diane Lewis, Connie Podesta, and Ulf Borg. For information contact TSRC Executive Office, PO Box 515239, Dallas TX 75251. (214) 239-8772 or fax (214) 239-6418.

July 12-14 in Vail, Colorado. The AARC presents the Summer Forum. See the April issue of *AARC Times* for more information or call the AARC Convention Department at (214) 243-2272.

July 28-29 in Las Vegas, Nevada. The NSRC will host its 5th Annual Meeting and Conference at the Howard Johnson Plaza-Suite Hotel. Contact Perri Tiggeman at (702) 361-1650 or (702) 643-6575.

August 7-9 in Albuquerque, New Mexico. Come help celebrate our Silver Anniversary at the Annual Summer Convention & Exhibition at the Albuquerque Holiday Inn-Pyramid. The NMSRC 4th Annual Golf Tournament is featured on August 7 at one of the country's top 50 public courses, Cochiti Lake. Contact Robert Quintela RRT RCP, Respiratory Therapy, St Joseph's West Mesa Hospital, 10501 Golf Course Road NW, Albuquerque NM 87106.

August 23 in Dayton, Ohio. The OSRC will present the fourth annual Neonatal/Pediatric Conference at Sinclair Center. Contact Susan Marcklinger, RRT, St Ann's Hospital of Columbus (614) 898-4069.

September 11-13 in Ocean City, Maryland. The MD/DC Society for Respiratory Care celebrates the 10th anniversary of its Conference by the Sea at the Carousel Hotel. Meeting topics include neonatal, critical care, pulmonary function testing, home care, rehab, and ethics, along with student and management workshops. Contact Elgloria Harrison at (202) 745-5105.

September 19-20 in Indianapolis, Indiana. The ISRC presents its 18th Annual Fall Seminar at the Holiday Inn-North. The two full days feature lectures, specialty sections, exhibits, and Sputum Bowl competitions. Topics include the future of ventilation, home care accreditation, pediatric rehabilitation, MDI therapy, total quality management, asthma, critical care, and Exosurf use. Contact Kathleen Lee, Ivy Tech, PO Box 1763, Indianapolis IN 46206. Or call (317) 921-4402.

September 25-27 in Minneapolis, Minnesota. The MSRC presents its 22nd Annual Education Conference at the Holiday Inn West. Activities begin with the 3rd annual "Duffers Open" golf tournament and the MSRC "Quiz Bowl." Dr Ronald Cranford, nationally known biomedical ethicist, gives the keynote lecture. Contact Michele Patnaude at (612) 347-2546.

October 30-31 in Sturbridge, Massachusetts. The MSRC presents its 14th Annual Meeting at the Sheraton Sturbridge Resort and Conference Center. Topics include bronchoscopy, home care, asthma diagnosis and therapy, ECMO, sleep studies, and much more. Special feature — Debate covering the pros and cons of pentamidine and ribavirin. Contact Gina Farquharson RRT, 16 Bartlett St, Pembroke MA 02359. (617) 293-6090.

OTHER MEETINGS

September 20 in Beaumont, Texas. The Respiratory Care Services Department of St Elizabeth Hospital hosts its 3rd Annual Educational Seminar at the Beaumont Plaza Holiday Inn. Lectures and hands-on workshops cover a wide variety of topics of interest to respiratory and nursing professionals. Contact Greg Rodgers RRT at (409) 899-7065.

September 27 in Philadelphia, Pennsylvania. Main Line Health Inc presents "Current Perspectives in Adult and Neonatal Pulmonary Care" at the Society Hill Sheraton Hotel. Fee: $100 physicians; $75 RTs, RNs, and PAs (includes breakfast and lunch). Hotel and tour packages available. Contact Bob Kay or Bill Howell, Bryn Mawr Hospital, 130 S Bryn Mawr Ave, Bryn Mawr PA 19010, (215) 526-3340.

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Application Deadline:	August 1, 1991

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RESPIRATORY CARE

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General Requirements

Submissions should (1) be related to respiratory care, (2) be planned for one of the publication categories below, and (3) be prepared as indicated in these Instructions. A letter accompanying the manuscript must specify the intended publication category, be signed by all the authors, and, when there are two or more authors, state that "We, the undersigned, have all participated in the work reported, read the accompanying manuscript, and approved its submission for publication."

Publication Categories

Research Article (Study): A report of an original investigation.
Evaluation of a Device/Method/Technique: A description and evaluation of an old or new device, method, technique, or modification.
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Case Series: Like a Case Report but including a number of cases.
Review Article: A comprehensive, critical review of the literature and state of the art of a pertinent topic that has been the subject of 40 or more published research papers.
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General Concerns—*Typist*

- Double-space ALL lines, including those in references, figure legends, and tables. Do not justify right margins.
- Number pages in upper right corner and leave margins of 1½" or more on all four sides of the page.
- For research articles, follow format of Model Manuscript, Respir Care 1984;29:182 (Feb 1984).
- Meticulously follow instructions for typing references.

General Concerns—*Author:*

- Structure manuscript as specified hereafter.
- Provide all requested information on title page as specified hereafter.
- Proofread manuscript for completeness, clarity, grammar, spelling; be sure all references, figures, and tables are cited in the text.
- Consider having paper reviewed in-house before submission.
- Have all co-authors proofread and approve manuscript and sign submission letter.

Manuscript Structure

Most kinds of papers have standard parts in a standard order. However, papers can vary individually, and not every paper will have all the parts listed here.

Research Article: Title page, abstract page, continuous text (Introduction, Materials & Methods, Results, Discussion), Product Sources page, Acknowledgments page, references, tables, figure legends. Please consult "Writing a Research Paper," Respir Care 1985;30:1057 (Dec 1985) and Model Manuscript, Respir Care 1984;29:182 (Feb 1984).
Evaluation of Device/Method/Technique: Title page, abstract page, continuous text (Introduction, Description of Device/Method/Technique, Methods of Evaluation, Results of Evaluation, Discussion), Product Sources page, Acknowledgments page, references, tables, figure legends.
Case Report or Case Series: Title page, abstract page, continuous text (Introduction, Case Summary, Discussion), Acknowledgments page, references, tables, figure legends. Also see "How To Write a Better Case Report," Respir Care 1982;27:29 (Jan 1982).
Review Article: Title page, Table of Contents page, continuous text (Introduction, History, Review of Literature, State of the Art, Discussion, Summary), references. May include figures & tables. No abstract. Table of Contents optional. Other formats may be appropriate.
Overview, Update, Point of View, or Special Article: Title page, text (introduction, message), references, tables, figure legends. No abstract.
Letter: Title page (provide a title), text, writer's name & affiliation, references. Tables & figures may be included. Double-space everything. Write "For Publication" on title page.

Structure: Important Details

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Abstract Page: Number this Page 1. List paper's title but omit authors' names. Abstract should be 200 words or less and must be informative, briefly specifying main points of paper, such as methods, results, and conclusions drawn.

Statistical Analysis: In research articles, identify statistical tests and chosen level of significance in the Methods section. In Results section, report actual P values.

Figures (illustrations): All photographs, diagrams, & graphs must be numbered as Figure 1, Figure 2, etc, according to the order in which each is first mentioned in the text. Photographs must be glossy prints 5 × 7 to 8 × 10 inches and should be black & white unless color is essential. Letters and numerals must be neat and large enough to remain legible if figure is reduced in size for publication. Final figures must be of professional quality, but 'rough' sketches may accompany the submitted manuscript, with final figures to be prepared after review. Identify each figure on back with a stick-on label showing figure number and arrow indicating top; omit author's name. Cover label with clear tape so ink will not smudge other prints. Supply three sets of unmounted figures. If figure has been published before, include copyright-holder's written permission to use it.

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Units of Measurement: In addition to conventional units of measure, show SI values and units in brackets after conventional expressions: ie, "PEEP, 10 cm H_2O [0.981 kPa]." For conversion to SI, see RESPIRATORY CARE 1988;33:861-873 (Oct 1988).

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References:

- Use references to support statements of fact, indicate sources of information, or guide readers to further pertinent literature.
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- In the text, cite references by superscript numerals (half space above text), not in parentheses. The first reference cited in the text is number 1, the next is number 2, etc.
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- Type references in medical-journal style. Examples appear at the end of these Instructions. Abbreviate journal names as in *Index Medicus*. A list of many journal-name abbreviations was published in Respir Care 1988;33:1050 (Nov 1988).
- DOUBLE-SPACE the lines of references.
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Standard Journal Article:

1. Shepherd KE, Johnson DC. Bronchodilator testing: An analysis of paradoxical responses. Respir Care 1988;33:667-671.

Corporate Author Journal Article:

2. American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33:1044-1046.

Article in Journal Supplement:

(Journals differ in their methods of numbering and identifying supplements. Supply sufficient information to allow retrieval.)

3. Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986;89(3, suppl):139s-143s.

Abstract in Journal:

(Abstracts are not strong references; when possible, full papers should be cited. When cited, abstracts should be identified as such.)

4. Lippard DL, Myers TF, Kahn SE. Accuracy of pulse oximetry in severely hypoxic infants (abstract). Respir Care 1988;33:886.

Editorial in Journal:

5. Rochester DF. Does respiratory muscle rest relieve fatigue or incipent fatigue? (editorial). Am Rev Respir Dis 1988;138:516-517.

Letter in Journal:

6. Smith DE, Herd D, Gazzard BG. Reversible bronchoconstriction with nebulised pentamidine (letter). Lancet 1988;2:905.

Personal Author Book:

7. Nunn JF. Applied respiratory physiology. New York: Appleton-Century-Crofts, 1969.

Note: To specify pages cited in a book, place a colon after the year and then list the page(s). Examples: 1969:85 (one page), 1963:85-95 (series of contiguous pages), 1963:85,95 (separated pages).

Corporate Author Book:

8. American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group, 1977.

Book with Editor, Compiler, or Chairman as 'Author':

9. Guenter CA, Welch MH, eds. Pulmonary medicine. Philadelphia: JB Lippincott, 1977.

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10. Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, eds. Pulmonary medicine. Philadelphia: JB Lippincott, 1977:171-223.

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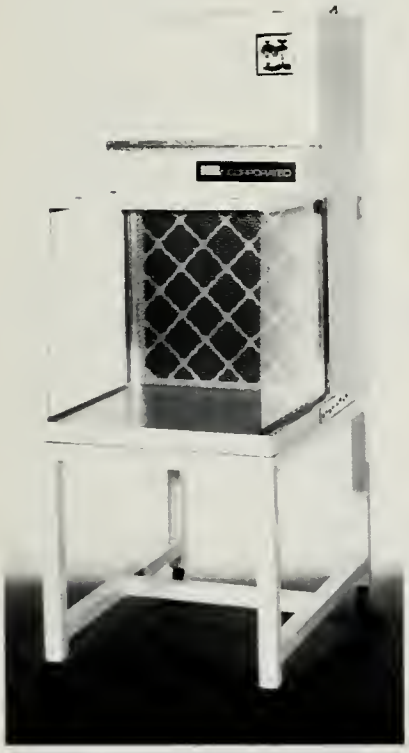

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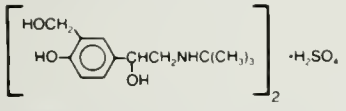
Proventil®
(albuterol sulfate)
Solution for Inhalation
Unit Dose 0.083%*
0.5%* 20 mL bottle
*Potency expressed as albuterol

DESCRIPTION PROVENTIL, brand of albuterol sulfate, Solution for Inhalation, is a relatively selective beta$_2$-adrenergic bronchodilator (see **CLINICAL PHARMACOLOGY** section below). Albuterol sulfate has the chemical name α^1-[(*tert*-Butylamino) methyl]-4-hydroxy-*m*-xylene-α,α'-diol sulfate (2:1) (salt), and the following chemical structure



Albuterol sulfate has a molecular weight of 576.7 and the empirical formula $(C_{13}H_{21}NO_3)_2{\cdot}H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol.

The international generic name for albuterol base is salbutamol.

PROVENTIL Solution for Inhalation is available in two concentrations. The 0.5% solution is in concentrated form. Dilute 0.5 mL of the solution to 3 mL with normal saline solution prior to administration. The 0.083% solution requires no dilution prior to administration.

Each mL of PROVENTIL Solution for Inhalation (0.5%) contains 5 mg of albuterol (as 6.0 mg of albuterol sulfate) in an aqueous solution containing benzalkonium chloride, sulfuric acid is used to adjust the pH between 3 and 5. PROVENTIL Solution for Inhalation (0.5%) contains no sulfiting agents. It is supplied in 20 mL bottles.

Each mL of PROVENTIL Solution for Inhalation (0.083%) contains 0.83 mg of albuterol (as 1.0 mg of albuterol sulfate) in an isotonic aqueous solution containing sodium chloride and benzalkonium chloride; sulfuric acid is used to adjust the pH between 3 and 5. PROVENTIL Solution for Inhalation (0.083%) contains no sulfiting agents. It is supplied in 3 mL bottles for unit-dose dispensing.

PROVENTIL Solution for Inhalation is a clear, colorless to light yellow solution.

CLINICAL PHARMACOLOGY The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that 10 to 50% of the beta receptors in the human heart may be beta$_2$ receptors. The precise function of these receptors, however, is not yet established. Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Studies in asthmatic patients have shown that less than 20% of a single albuterol dose was absorbed following either IPPB or nebulizer administration, the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. Following a 3.0 mg dose of nebulized albuterol, the maximum albuterol plasma level at 0.5 hour was 2.1 ng/mL (range 1.4 to 3.2 ng/mL). There was a significant dose-related response in FEV_1 and peak flow rate (PFR). It has been demonstrated that following oral administration of 4 mg albuterol, the elimination half-life was 5 to 6 hours.

Animal studies show that albuterol does not pass the blood-brain barrier. Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

In controlled clinical trials, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by FEV_1. FEV_1 measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer, and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in FEV_1 over baseline values) continued for 3 to 4 hours in most patients and in some patients continued up to 6 hours.

In repetitive dose studies, continued effectiveness was demonstrated throughout the 3-month period of treatment in some patients.

INDICATIONS AND USAGE PROVENTIL Solution for Inhalation is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm.

CONTRAINDICATIONS PROVENTIL Solution for Inhalation is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS As with other inhaled beta-adrenergic agonists, PROVENTIL Solution for Inhalation can produce paradoxical bronchospasm, which can be life threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of sympathomimetic nebulizers. It is, therefore, essential that the physician instruct the patient in the need for further evaluation if his/her asthma becomes worse. In individual patients, any beta$_2$-adrenergic agonist, including albuterol solution for inhalation, may have a clinically significant cardiac effect.

Immediate hypersensitivity reactions may occur after administration of albuterol as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

PRECAUTIONS General: Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension, in patients with convulsive disorders, hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Additionally, beta-agonists, including albuterol, when given intravenously may cause a decrease in serum potassium, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation. The relevance of these observations to the use of PROVENTIL Solution for Inhalation is unknown.

Information For Patients: The action of PROVENTIL Solution for Inhalation may last up to 6 hours and therefore it should not be used more frequently than recommended. Do not increase the dose or frequency of medication without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking PROVENTIL Solution for Inhalation, other antiasthma medicines should not be used unless prescribed.

Drug Interactions: Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat, at oral doses corresponding to 10, 50, and 250 times the maximum human nebulizer dose. In another study, this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Teratogenic Effects–Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given subcutaneously in doses corresponding to the human nebulization dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 0.1, 1, and 12.5 times the maximum human nebulization dose, respectively) showed cleft palate formation in 5 of 111 (4.5%) of fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) of fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) of fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) of fetuses at 50 mg/kg, corresponding to 250 times the maximum human nebulization dose.

Labor and Delivery: Oral albuterol has been shown to delay preterm labor in some reports. There are presently no well-controlled studies which demonstrate that it will stop preterm labor or prevent labor at term. Therefore, cautious use of PROVENTIL Solution for Inhalation is required in pregnant patients when given for relief of bronchospasm so as to avoid interference with uterine contractibility.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of albuterol solution for inhalation in children below the age of 12 years have not been established.

ADVERSE REACTIONS The results of clinical trials with PROVENTIL Solution for Inhalation in 135 patients showed the following side effects which were considered probably or possibly drug related:

Central Nervous System tremors (20%), dizziness (7%), nervousness (4%), headache (3%), insomnia (1%)

Gastrointestinal nausea (4%), dyspepsia (1%)

Ear, Nose and Throat pharyngitis (<1%), nasal congestion (1%)

Cardiovascular tachycardia (1%), hypertension (1%)

Respiratory bronchospasm (8%), cough (4%), bronchitis (4%), wheezing (1%)

No clinically relevant laboratory abnormalities related to PROVENTIL Solution for Inhalation administration were determined in these studies.

In comparing the adverse reactions reported for patients treated with PROVENTIL Solution for Inhalation with those of patients treated with isoproterenol during clinical trials of 3 months, the following moderate to severe reactions, as judged by the investigators, were reported. This table does not include mild reactions.

Percent Incidence of Moderate To Severe Adverse Reactions

Reaction	Albuterol N = 65	Isoproterenol N = 65
Central Nervous System		
Tremors	10.7%	13.8%
Headache	3.1%	1.5%
Insomnia	3.1%	1.5%
Cardiovascular		
Hypertension	3.1%	3.1%
Arrhythmias	0%	3.0%
**Palpitation	0%	22.0%
Respiratory		
*Bronchospasm	15.4%	18%
Cough	3.1%	5%
Bronchitis	1.5%	5%
Wheeze	1.5%	1.5%
Sputum Increase	1.5%	1.5%
Dyspnea	1.5%	1.5%
Gastrointestinal		
Nausea	3.1%	0
Dyspepsia	1.5%	0
Systemic		
Malaise	1.5%	0

*In most cases of bronchospasm, this term was generally used to describe exacerbations in the underlying pulmonary disease.

**The finding of no arrhythmias and no palpitations after albuterol administration in this clinical study should not be interpreted as indicating that these adverse effects cannot occur after the administration of inhaled albuterol.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol.

OVERDOSAGE Manifestations of overdosage may include anginal pain, hypertension, hypokalemia, and exaggeration of the pharmacological effects listed in **ADVERSE REACTIONS.**

The oral LD_{50} in rats and mice was greater than 2,000 mg/kg. The inhalational LD_{50} could not be determined.

There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROVENTIL Solution for Inhalation.

DOSAGE AND ADMINISTRATION The usual dosage for adults and children 12 years and older is 2.5 mg of albuterol administered 3 to 4 times daily by nebulization. More frequent administration or higher doses is not recommended. To administer 2.5 mg of albuterol, either dilute 0.5 mL of the 0.5% solution for inhalation to a total volume of 3 mL with normal saline solution, or administer the contents of one unit-dose bottle (3 mL of 0.083% nebulizer solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that the PROVENTIL Solution for Inhalation will be delivered over approximately 5 to 15 minutes.

The use of PROVENTIL Solution for Inhalation can be continued as medically indicated to control recurring bouts of bronchospasm. During treatment, most patients gain optimum benefit from regular use of the nebulizer solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

HOW SUPPLIED PROVENTIL Solution for Inhalation, 0.5%, is a clear, colorless to light yellow solution, and is supplied in bottles of 20 mL (NDC-0085-0208-02) with accompanying calibrated dropper, boxes of one. **Store between 2° and 25°C (36° and 77°F).**

PROVENTIL Solution for Inhalation, 0.083%, is a clear, colorless to light yellow solution, and is supplied in unit-dose bottles of 3 mL each, boxes of 25 (NDC-0085-0209-01.) **Store between 2° and 25°C (36° and 77°F).**

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